FORMULATION DEVELOPMENT AND EVALUATION OF BILYER TABLETS OF LISINOPRIL FOR IMMEDIATE RELEASE AND GLIPIZIDE FOR SUSTAINED RELEASE

A Dissertation submitted to

THE TAMILNADU DR.M.G.R.MEDICAL UNIVERSITY
CHENNAI - 600 032.

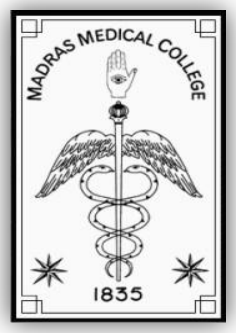
In partial fulfilment of the requirements for the award of the degree of

MASTER OF PHARMACY
IN
PHARMACEUTICS

Submitted by
Reg. No. 261211256
Under the Guidance of

Mrs. R. Devi Damayanthi, M.Pharm.,

Tutor in Pharmacy
Department of Pharmaceutics



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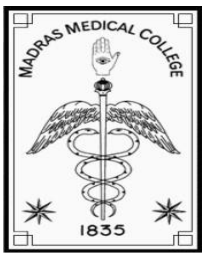

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Evaluated.

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Place: Chennai-03.

Date: (Dr.A.Jerad Suresh)

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Place: Chennai-03.

Date: (Prof. K.Elango)

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Place: Chennai-03.

Date: (R. Devi Damayanthi)

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"Gratitude makes sense of our past, brings peace for today and creates a vision for tomorrow"

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Dedicated To

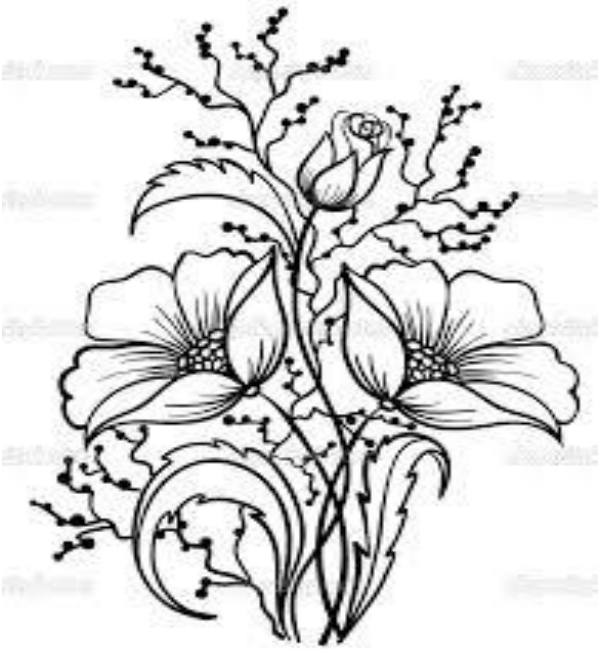
My Family & My Profession

LIST OF ABBREVIATIONS USED

API	: Active Pharmaceutical Ingredient
ACE	: Angiotensin Converting Enzyme
BCS	: Biopharmaceutical Classification System
BP	: British Pharmacopoeia
B	: Beta
C	: Celsius
CR	: Controlled Release
Conc.	: Concentration
Cm	: Centimeter
Cum.	: Cumulative
dL	: Decilitre
DM	: Diabetes Mellitus
EC	: Ethyl Cellulose
et al	: and others
Fig.	: Figure
FTIR	: Fourier Transform Infra Red
λ	: Lamda
g	: gram
GMP	: Good Manufacturing Practice
hrs	: hours
HCl	: Hydrochloric Acid
HPMC	: Hydroxy Propyl Methyl Cellulose
i.e.	: that is
IP	: Indian Pharmacopoeia
IPA	: Isopropyl Alcohol
IR	: Immediate Release

ICH	: International Conference on Harmonization
JP	: Japanese Pharmacopoeia
KBr	: Potassium Bromide
M	: Molar
MCC	: Micro Crystalline Cellulose
mg	: milligram
mm	: millimeter
ml	: milliliter
mins	: minutes
µg	: microgram
NaOH	: Sodium hydroxide
nm	: nanometer
pH	:Negative logarithm of hydrogen ion concentration
Ph Eur	: European Pharmacopoeia
PVP	: Poly Vinyl Pyrrolidone
rpm	: revolutions per minute
R^2	: Correlation factor
RH	: Relative Humidity
SD	: Standard Deviation
Sec.	: Seconds
SSG	: Sodium Starch Glycolate
SR	: Sustained Release
$t_{1/2}$	: Half life
UV	: Ultra Violet
v	: Volume
w	: Weight

Contents



Introduction

1. INTRODUCTION

HEALTH

Health is a level of functional and metabolic efficiency of a living organism. In humans, it is a general condition of a person's mind and body, usually meaning to be free from illness, injury or pain. The world health organization defined health in its broader sense in 1946 as a state of complete physical, mental and social well being and not merely absence of disease or infirmity. Systematic activities to prevent or cure health problems and promote good health in humans are undertaken by health care providers.[1, 2]

DOSAGE FORMS

Dosage forms are essentially pharmaceutical products in the form in which they are marketed for use, typically involving a mixture of active drug components and nondrug components, along with other non reusable material that may not be considered either ingredient or packing.

Depending upon the method/route of administration, dosage forms come in several types. These include many kinds of liquid, solid and semisolid dosage forms.[3]

ORAL SOLID DOSAGE FORM

The convenient oral drug delivery has been known for decades as the most widely used route of administration among all the routes. It remains the preferred route of administration in the discovery and development of new drug candidates. The popularity of oral route is attributed to patient acceptance, ease of administration, accurate dosing, and cost effective manufacturing methods and generally improved shelf life of the product.

Oral solid dosage forms such as tablets and capsules have been formulated and developed nowadays since they are the most effective routes of administration of a new drug. Pharmaceutical products designed for oral delivery and currently available on the prescription and over the counter markets are mostly the immediate release type, which are designed for immediate release of drug for rapid absorption. Many new generations of pharmaceutical products called controlled and sustained release drug delivery systems have also been developed. So the combination of both will be very much useful for immediate response and for maintaining the duration of action.[3]

TABLETS

Tablets are solid dosage forms each containing a unit dose of one or more medicaments. They are intended for oral administration. Some tablets are swallowed whole or after being chewed, some are dissolved or dispersed in water before administration and some are retained in the mouth where the active ingredient is liberated.

According to Indian pharmacopoeia, pharmaceutical Tablets are usually solids, flat or biconvex, unit dosage form, prepared by compressing a drug or mixture of drugs, with or without diluents. They vary in shapes like triangular, rectangular etc. and differ greatly in size and weight, depending on the amount of medical substances and the intended mode of administration. It is the most popular dosage form and 70% of the total medicines are dispensed in the form of tablet. They may have lines or break-marks and may bear a symbol or other markings. Tablets may be coated or uncoated. They are sufficiently hard to withstand handling without crumbling or breaking.[4]

ADVANTAGES OF TABLET MEDICATION[5]

- They are the unit dosage form and offer the greatest capabilities of all oral dosage forms for the greatest dose precision and least content variability.
- Low cost among all oral dosage forms.
- They are the most compact dosage forms.
- They are the easiest and cheapest to package and ship.
- Product identification requires no additional processing steps when employing an embossed or monogrammed punch face.
- Provides greatest ease of swallowing with the least tendency for hang up above the stomach, especially when coated provided the tablet disintegration is not excessively rapid.
- They lend themselves to certain special release profile products e.g. enteric coated delayed release profiles.
- Easy large scale production than other oral dosage forms.

- They have the best combined properties of chemical, mechanical and microbiological stability among all the oral dosage forms.
- The emergency supplies of the drug can be conveniently carried by the patient.

DISADVANTAGES[5]

- Some drugs have resistance for compression into dense compacts, owing to their amorphous nature or flocculent, low density properties.
- Drugs with better taste, objectionable odour, sensitivity towards oxygen or hygroscopic nature may require encapsulation/entrapment prior to compression, or coating of tablets is required.
- Elderly, ill and children could have problem in swallowing the tablets.
- Drugs with poor wetting and slow dissolution properties may be difficult to formulate or manufacture as a tablet that will still provide adequate or full drug bioavailability.

TYPES OF TABLETS[6]

Tablets are divided into classes based on their route of administration and their function.

1. **TABLETS ADMINISTERD ORALLY**
   - **A. Compressed tablets**
     - Sugar coated tablets
     - Film coated tablets
     - Enteric coated tablets
     - Chewable tablets
     - Controlled release tablets
   - **B. Multiple compressed tablets**
     - Layered tablets
     - Press coated tablets
2. **TABLETS ADMINISTERED IN ORAL CAVITY**
   - A. Buccal and sublingual tablets
   - B. Lozenges and trouches
   - C. Dental cones
3. **TABLETS ADMINISTERED VIA OTHER ROUTES**
   - A. Implants
   - B. Compressed suppositories or inserts
   - C. Vaginal tablet

4. **TABLETS ADMINISTERED IN SOLUTION FORM**
   A. Effervescent tablets
   B. Dispensing tablets
   C. Hypodermic tablets
   D. Tablet triturates

MULTILAYER TABLETS

Multilayer tablets are made by compressing several different granulations fed into die in succession, one on top of another, in layers. Each layer comes from a separate feed frame with individual weight control. Rotary tablet process can be set up for two or three layers. More are possible but the design becomes very special. Ideally, a slight compression of each layer and individual layer ejection permits weight checking for control purpose.

ADVANTAGES OF MULTILAYER TABLETS

- Incompatible substances can be separated by formulating them in separate layers as a two-layer tablet or separating the two layers by a third layer of an inert substance as a barrier between the two.
- Two layer tablets may be designed for sustained release one layer for immediate release of the drug and the second layer for extended release, thus maintain a prolonged blood level.
- Layers may be coloured differently to identify the product.

BILAYER TABLET[7]

Bi-layer tablet is a unit compressed tablet dosage form intended for oral application. It contains two layers in which one layer having conventional or immediate release part of single or multiple active ingredients, another layer is sustained or controlled release part of single or multiple active ingredients.

Bi-layer tablets are novel drug delivery system where combination of two or more drugs in single unit having different release profiles improves the patient compliance, prolongs the drug action, resulting in effective therapy along with better control of plasma drug level.

Bi-layer tablet is suitable for sequential release of two drugs in combination, separate two incompatible substances, and also for sustained release tablet in which one layer is immediate release as initial dose and second layer is maintenance dose.

Nowadays various developed and developing countries move towards combination therapy for treatment of various diseases and disorders requiring long term therapy such as hypertension, diabetes and cardiovascular diseases. Combination preparation plays an important role in clinical treatment because of its better and wider curative synergism and weaker side effects. Combination therapy may be achieved by giving separate drugs or where available by giving combination drugs (monolithic or bilayer dosage form) which are dosage forms that contain more than one active ingredient.

ADVANTAGES

They are used as an extension of a conventional technology

- Ability to combine different release rate. IR and SR in the same tablet for chronic condition requiring repeated dosing.
- Promoting patient convenience and compliance because fewer daily doses are required compared to traditional delivery system.
- Two different drugs in same dosage form.
- Separation of incompatible components thus minimizes the physical and chemical incompatibilities.
- Solve degradation problem.
- Reduce pill burden to patient.
- Maintain physical and chemical stability.
- Retain potency and ensure dose accuracy.

ADVANTAGES OF BI-LAYER TABLETS OVER CONVENTIONAL TABLETS

- Blood level of drug can be held at consistent therapeutic level for improved drug deliver, accuracy, safety and reduce side effects. Reduction of adverse side effects can be accomplished by targeting the drug release to the absorption site as well as controlling the rate of release, enabling the total drug content to be reduced.
- Patient convenience is improved by fewer daily doses are required compared to traditional system. Patient compliance is enhanced leading to improved drug regimen efficacy.

- Bilayer tablets are readily lend themselves to repeat action products, where in one layer on layered tablet provides the initial dose, rapidly disintegration in the stomach, the layer are insoluble in gastric media but released in the intestinal environment.
- Separate physically and chemically incompatible ingredients.

DISADVANTAGES

- Inaccurate individual layer weight control.
- Cross contamination between the layers.
- Insufficient hardness.
- Reduced yield.
- Adds complexity and bi-layer rotary presses are expensive.

TYPES OF BILAYER TABLET PRESS

1. Single sided tablet press
2. Double sided tablet press
3. Bi-layer tablet press with displacement monitoring

SINGLE SIDED TABLET PRESS

- The simplest design is a single sided press with both chambers of the doublet feeder separated from each other.
- Each chamber is gravity or force fed with different powers, thus producing the individual layers of the tablets.
- When the die passes under the feeder, it is at first loaded with the first layer powder followed by the second layer powder.
- Then the entire tablet is compressed in one or two steps.

LIMITATIONS

- No weight monitoring/control of the individual layers.
- No distinct visual separation between the two layers.
- Very short first layer dwell time due to the small compression roller, possibly resulting in poor de-aeration, capping and hardness problems.
- This may be corrected by reducing the turret-rotation speed (to extend the dwell time) but with the consequence of lower tablet output.

- Very difficult first layer tablet sampling and sample transport to a test unit for in-line quality control and weight recalibration.

DOUBLE SIDED TABLET PRESS

- Most double sided tablet presses with automated production control use compression force to monitor and control tablet weight.
- The effective peak compression force exerted on each individual tablet or layer is measured by the control system at the main compression of the layer.
- This measured peak compression force is the signal used by the control system to reject out of tolerance tablets and correct the die fill depth when required.

BILAYER TABLET PRESS WITH DISPLACEMENT

The displacement tablet weight control principle is fundamentally different from the principle based upon compression force. When measuring displacement, the control system sensitivity does not depend on the tablet weight but depends on the applied pre-compression force.

ADVANTAGES

- Weight monitoring/control for accurate and independent weight control of the individual layers.
- Low compression force exerted on the first layer to avoid capping and separation of the two individual layers.
- Independence from machine stiffness.
- Increased dwell time at pre-compression of both first and second layer to provide sufficient hardness at maximum turret speed.
- Maximum prevention of cross contamination between the two layers.
- Clear visual separation between the two layers and maximized yield.

VARIOUS TECHNIQUES FO A BI-LAYER TABLET[7,8]

The techniques are as follows,

1. OROS® push pull technology
2. L-OROS tm technology
3. EN SO TROL technology

4. DUROS technology
5. DUREDAS^{TM} technology

1. OROS ® push pull technology

This system consist of mainly two or three layers among which one or more layers are the drug and other layer consist of push layer. The drug layer mainly consists of drug along with two or more different ingredients. The drug layer consists of poorly soluble drug. There is further addition of suspending agent and osmotic agent. A semi permeable layer surrounds the tablet core.

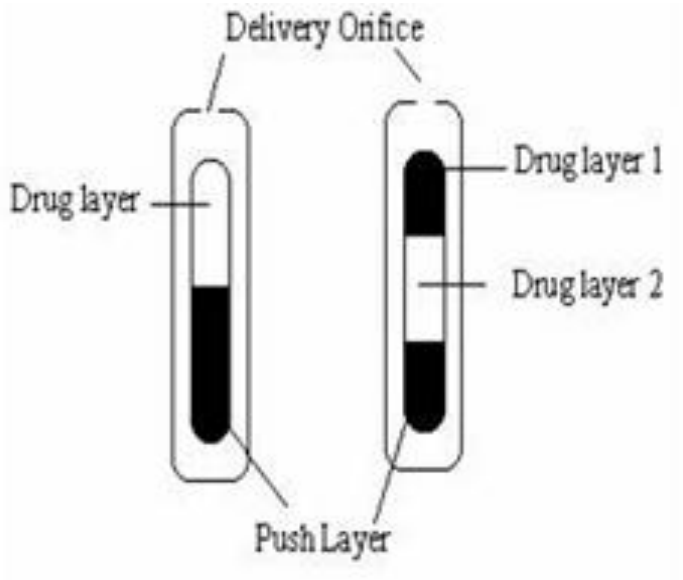


Fig 1: Bilayer and trilayer OROS push pull technology

2. L-OROS tm technology

This system is used for the solubility issue. Alza developed the L-OROS system where a lipid soft gel product containing drug in a dissolved state is initially manufactured and then coated with a barrier membrane, then osmotic push layer and then a semi permeable layer membrane drilled with an external orifice.

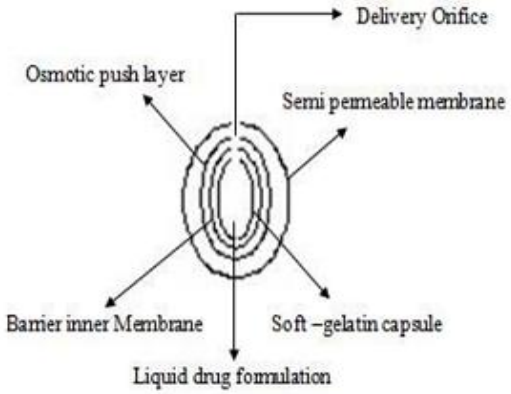


Fig 2: L –OROS tm technology

3. EN SO TROL technology

Solubility enhancement of an order of magnitude or to create optimized dosage form shire laboratory use an integrated approach to drug delivery focusing on identification and incorporation of the identified enhancer into controlled release technologies.

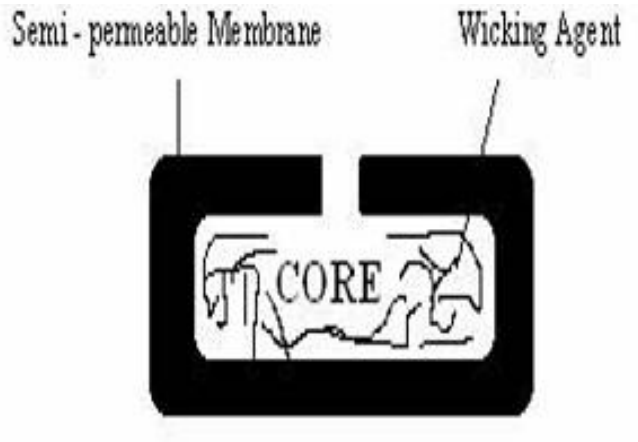


Fig 3: EN SO TROL technology

4. DUROS technology

The system consists of an outer cylindrical titanium alloy reservoir. The reservoir has high impact strength and protects the drug molecules from enzymes. The DUROS technology is the miniature drug dispensing system that opposes like a miniature syringe and release minute quantity of concentrated form in continuous and consistent form over months or years.

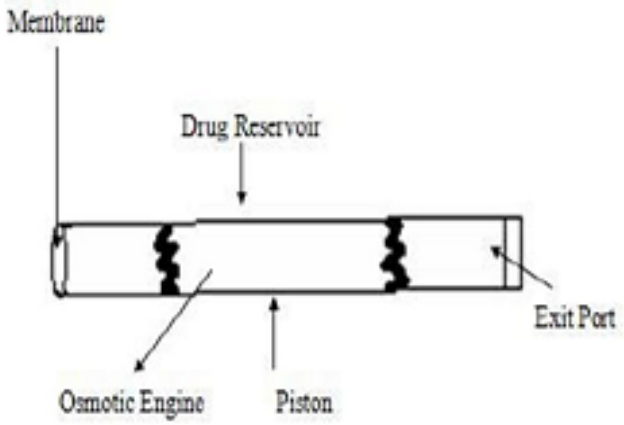


Fig 4: DUROS technology

6. DUREDAS™ technology

It is a bilayer tablet which can provide immediate or sustained release of two drugs or different release rate of the same drug in one dosage form. The tabletting process can provide an immediate release granulate and a modified release hydrophilic matrix complex as separate layers within one tablet. The modified release properties of the dosage form are provided by a combination of hydrophilic polymers.

Benefits offered by the DUREDAS™ technology includes

- Bilayer tabletting technology
- Tailored release rate of two drug components
- Capability of two different CR formulations combined
- Capability for immediate release and modified release components in one tablet
- Unit dose, tablet presentation

The DUREDAS™system can be easily manipulated to allow incorporation of two controlled release formulation on the bi-layer. Two different release rates can be achieved from each side. In this way greater prolongation of sustained release can be achieved.

Typically an immediate release granule is compressed first followed by the addition of a controlled/sustained release element which is compressed onto the initial tablet. This gives the characteristic bi-layer effect to the final dosage form.

A further extension of DUREDAS™ technology is the production of controlled release dosage forms where by two drugs are incorporated into the different layers and drug

release of each is controlled to maximize the therapeutic effect of the combination. Again both immediate and controlled release combinations of two drugs are possible.

PRECAUTIONS TO BE TAKEN TO GET GOOD BILAYER TABLETS

For good quality tablets with sharp definition between the layers, special care must be taken as follows.

- Dust fines must be limited. Fines smaller than 100 mesh should be kept at a minimum.
- Maximum granule size should be less than 16 mesh for a smooth, uniform scrape-off at the die.
- Materials that smear, chalk or coat on the die table must be avoided to obtain clean scrape-off and uncontaminated layers.
- Low moisture is essential if incompatibles are used.
- Weak granules that break down easily must be avoided. Excessive amounts of lubrication especially metallic stearates should be avoided for better adhesion of the layers.
- Formulation of multilayer tablet is more demanding than that of single layer tablets. For this reason, selection of additives is critical.

IMMEDIATE RELEASE TABLETS[9]

The term "immediate release" pharmaceutical formulation includes any formulation in which the rate of release of drug from the formulation and/or the absorption of drug, is neither appreciably, nor intentionally, retarded by galenic manipulations. In the present case, immediate release may be provided for by way of an appropriate pharmaceutically acceptable diluent or carrier, which diluent or carrier does not prolong, to an appreciable extent, the rate of drug release and/or absorption.

Immediate release dosage forms are those for which >85% of the labeled amount dissolves within 30minutes. For immediate release tablets, the only barrier to drug release is disintegration or erosion stage which is generally accomplished in less than one hour. To enhance dissolution and hence bioavailability of any drug for immediate release tablets, disintegration is one of the important process. Few super disintegrants are available commercially as croscarmellose sodium, crospovidone and sodium starch glycolate.

Tablets for an immediate release often consist of filler, binder, lubricant and disintegrant. In many cases, the disintegration time of solid dosage form is too long to provide appropriate therapeutic effect. To improve the disintegration time, disintegrants are used. The most accepted mechanisms of their action are wicking, swelling, and deformation recovery and particle repulsion. Together, these phenomena create a disintegrating force within the matrix. In the past, non modified disintegrants like alginates, starches, amberlite resins, cellulose materials, pectins and others were used to accelerate disintegration.

Today, a fast working superdisintegrant is chemically modified, typically by crosslinking the organic chains of a polymeric molecules. Three classes of super disintegrants are commonly used. Modified cellulose (croscarmellose sodium – Ac-Di-Sol®, Vivasol®), crosslinked polyvinyl-pyrrolidone (polyplasdone® XL – 10) and modified starch (sodium starch glycolate - Primojel®, Explotab®).

CONTROLLED DRUG DELIVERY SYSTEMS[10, 11]

It includes any drug delivery system which releases the drug predetermined rate over an extended period time.

Over the Past 30 years, as the expense and complications involved in marketing new drug entities have increased, with concomitant recognition of the therapeutic advantages of Sustained drug delivery, greater attention is being paid on development of oral sustained release drug delivery systems.

The goal in designing sustained release drug delivery system is to reduce the frequency of the dosing, reducing the dose & providing uniform drug delivery. So, Sustained release dosage form that releases one or more drugs continuously in predetermined pattern for a fixed period of time, either systemically or locally to specified target organ. Sustained release dosage forms provide better control of plasma drug levels, less dosage frequency, less side effect, increased efficacy and constant delivery.

This is usually accomplished by attempting to obtain zero order release from the dosage form. Zero order release constitutes drug release from the dosage form that is independent of the amount of the drug in the delivery system (i.e., a constant rate).

Sustained release generally do not attain this type of release and usually try to mimic zero order release providing drug in a slow first order fashion (i.e., concentration dependent).

Systems that are designated as prolonged release can be considered as attempts at achieving sustained release delivery. Repeat action tablets are a method of sustained release in which multiple doses of a drug are continued within the dosage form and each dose is released at a periodic interval. Delayed release systems, in contrast, may not be sustaining. Since often the function of these dosage forms is to maintain the drug within the dosage form for some time before release. Commonly the release rate is not alteredand does not result in sustained delivery, once drug release has begun. Enteric coated tablets are example of such type of dosage form.

Controlled release, although resulting in a zero order delivery system, may also incorporate methods to promote localization of the drug at an active site. In some cases, a controlled release system will not be sustaining, but will be concerned strictly with localization of the drug. Site-specific systems and targeted delivery systems are the descriptive terms used to denote this type of delivery control.

GENERAL PRINCIPLE OF CONTROLLED RELEASE SYSTEMS[12]

The ideal of providing an exact amount of drug at the site of action for a precise time period is usually approximated by most systems. This approximation is achieved by creating a constant concentration in the body or an organ over an extended period of time; in other words, the amount removed from the system. All forms of metabolism and excretion are included in the removal process: urinary excretion, entero hepatic recycling, sweats, faecal and so on. Since for most of the drugs these elimination processes are first order, it can be said that at certain blood level, the drug will have specific rate of elimination. This idea is to deliver drug at the exact rate for an extended period. This is represented mathematically as

$$\textbf{Rate in = Rate out =} K_{elim} \times C_d \times V_d$$

Where, $C_d$is the desired drug level, $V_d$is the volume of distribution and K_{elim} is the rate of drug elimination from the body. Often such exacting delivery proves to be difficult to achieve administration routes other than intravenous infusion. Non invasive routes (e.g., oral) are obviously preferred.

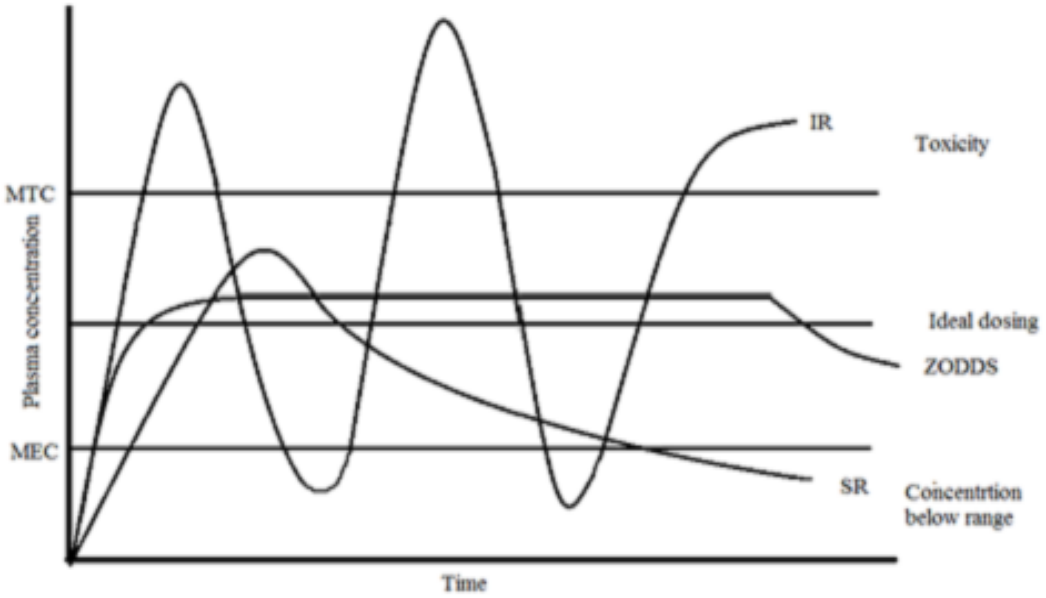


Fig 5: Ideal Plasma concentration versus time profile showing differences between zero order controlled release, slow first order sustained release, and immediate release.

The pharmacological effect is seen as long as the amount of drug is within the therapeutic range. Problems occur when peak concentration is above or below this range, especially for drugs with narrow therapeutic windows.

The slow first order release obtained by sustained release preparation is generally achieved by slowing the release of drug from a dosage form. In some cases this is accomplished by a continuous release process; however system that release small bursts of drug over a prolonged period can mimic the continuous system.

SUSTAINED RELEASE DRUG DELIVERY SYSTEM[14, 15]

It includes any drug delivery system achieves release of drug over an extended period of time, which not depend on time. Hydrophilic polymer matrix is widely used for formulating an Sustained dosage form. The role of ideal drug delivery system is to provide proper amount of drug at regular time interval & at right site of action to maintain therapeutic range of drug in blood plasma.

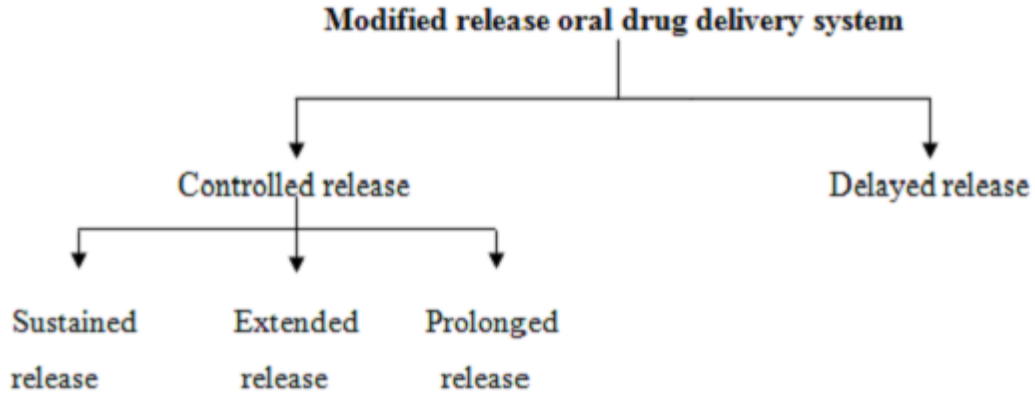


Fig 6: Formulation strategy for oral sustained release drug delivery system

The IR drug delivery system lacks some features like dose maintenance, sustained release rate & site targeting. The oral Sustained drug delivery has some potential advantage like Sustained release rate & dose maintenance in plasma. The SR formulations have some swelling polymer or waxes or both which controls the release rate. The use of reservoir system is also well known for controlling release rate. The IR drug delivery system lacks some features like dose maintenance, sustained release rate & site targeting. The oral Sustained drug delivery has some potential advantage like Sustained release rate & dose maintenance in plasma. The SR formulations have some swelling polymer or waxes or both which controls the release rate. The use of reservoir system is also well known for controlling release rate.

Advantages

Sustained/Controlled release products offer many potential benefits over the conventional dosage forms.

- Reduced dosing frequency.
- Dose reduction.
- Improved patient compliance.
- Constant level of drug concentration in blood plasma.
- Reduced toxicity due to overdose.
- Reduces the fluctuation of peak valley concentration.
- Night time dosing can be avoided.

Disadvantages

- Sustained release products contain a higher drug load and thus any loss of integrity of the release characteristics of the dosage form has potential problems.
- The larger size of sustained release products may cause difficulties in ingestion or transit through the gut.
- Sustained release products may cause decreased systemic bioavailability in comparison to conventional dosage forms, which may be due to incomplete release, increased first pass metabolism, increased instability, insufficient residence time for complete release, site specific absorption, pH dependent stability etc.
- Possibility of dose dumping due to food, physiologic or formulation variables or chewing or grinding of oral formulations by the patient and thus increased risk of toxicity.

RELEASE MECHANISM FOR SUSTAINED AND CONTROLLED RELEASE SYSTEM[13]

Based on the release mechanism these are classified as follows,

- Diffusion controlled system
- Dissolution controlled system

Diffusion controlled system

In these systems, there is a water soluble polymer, which controls the flow of water and the subsequent release of dissolved drug from the dosage form. Diffusion occurs when a drug passes through the polymer that forms the controlled release device. The diffusion can occur through the pores in the polymer matrix or by passing between polymer chains. These are broadly classified into two categories.

1. Diffusion reservoir system
2. Diffusion matrix system

The basic mechanisms of drug release from these two systems are fundamentally different.

Diffusion reservoir system

In this system, a water insoluble polymeric material covers a core of drug. Drug will partition into the membrane and exchange with the fluid surrounding the particle or tablet. Additional drug will enter the polymer, diffuse to the periphery and exchange with the surrounding media. The drug release takes place by diffusion mechanism.

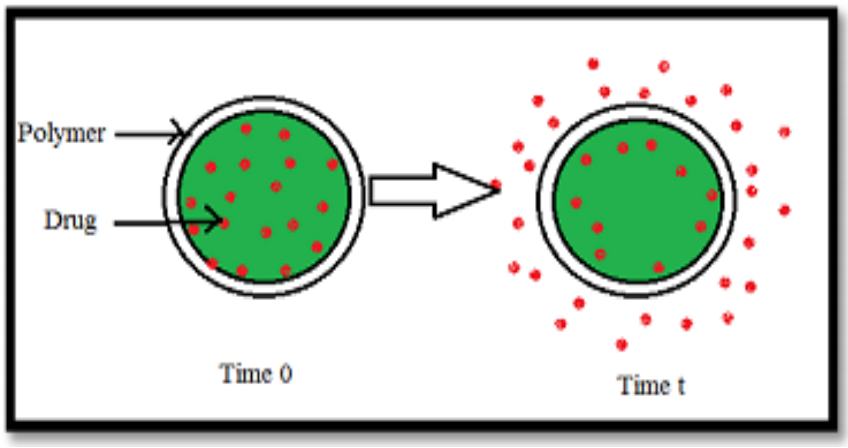


Fig 7:Schematic representation of diffusion type reservoir system

Diffusion matrix system

The matrix system is defined as a well-mixed composite of one or more drugs with gelling agent i.e. hydrophilic polymers. Matrix systems are widely used for sustaining the release rate.

It is the release system which prolongs and controls the release of the drug that is dissolved or dispersed. A solid drug is dispersed in an insoluble matrix and the rate of release of drug is dependent on the rate of drug diffusion and not on the rate of solid dissolution.

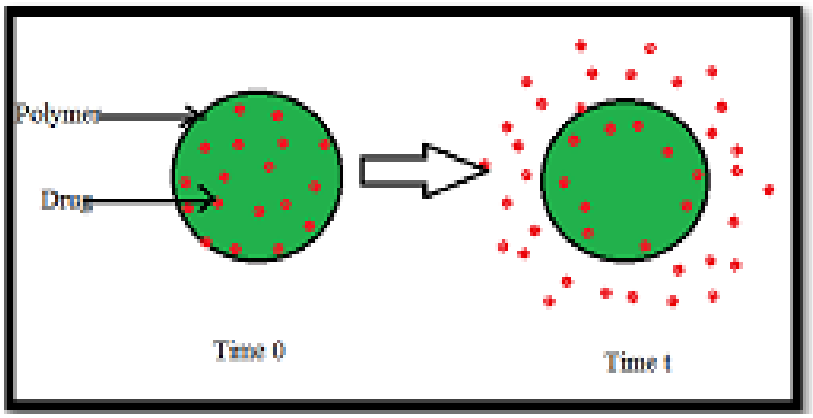


Fig 8: Schematic representation of diffusion matrix system

Dissolution controlled system

A drug with a slow dissolution rate is inherently sustained and for those drugs with high water solubility, one can decrease dissolution through appropriate salt or derivative formation. These systems are most commonly employed in the production of enteric coated dosage forms. To protect the stomach from the effects of drugs such as Aspirin, a coating that dissolves in natural or alkaline media is used. This inhibits release of drug from the dosage form until it reaches the higher pH of the intestine.

In most cases, enteric coated dosage forms are not truly sustaining in nature, but serve as a useful function in directing release of the drug to a required site. The same approach can be employed for compounds that are degraded by the harsh conditions found in the gastric region.

Literature Review

2. LITERATURE REVIEW

REVIEW FOR BILAYER TABLETS

1.Deepika K L *et al.*,[16] designed and evaluated the sustained release bilayer tablets of Domperidone Maleate. The tablets were prepared by wet granulation method using Croscarmellose sodium as super disintegrant for the immediate release layer and the hydrophilic matrix formers such as HPMC K4M, HPMC K 100 M and Carbopol 974 NF for the sustained release layer. Bilayer tablet showed as initial burst effect to provide dose of immediate release layer, followed by sustained release of Domperidone for 12 hours. The data obtained from in vitro release study were fitted to various mathematical model like zero order, First order, Higuchi model and Peppas model. The results of mathematical model fitting of data obtained indicated that, the best fit model in all the cases the release was found to be by diffusion and nonfickian release.

2. Kotta Kranthi Kumar *et al.*,[17] formulated and evaluated the sustained release bilayer tablets of Pioglitazone hydrochloride for immediate release using cross Povidone as super disintegrant and Metformin hydrochloride for sustained release using poly ethylene oxide (PEO-303) as matrix forming polymer. The tablets were prepared by direct compression technique and Wet granulation technique. The release kinetics of Metformin hydrochloride was evaluated using the regression coefficient analysis. The formulated tablets shows first order release and diffusion was the dominant mechanism of drug release. Thus formulated bilayer tablets proved immediate release of Pioglitazone and Metformin HCl as sustained release over a period of 12 hours.

3. Ashraful Islam S M *et al*., [18] formulated and evaluated of bilayer tablets consisting of Paracetamol and Aceclofenac for immediate drug release. Bilayer tablets are prepared by wet granulation technique by using sodium starch glycolate (SSG) as super disintegrant sodium lauryl sulphate (SLS) as surfactant to promote drug release. The amount of Paracetamol and Aceclofenac released at different time intervals were estimated by HPLC method. Dissolution results of all the tablet formulations were analyzed with dissolution efficiency (% DE). These results indicated that release of the drug from the tablet was influenced by content of super disintegrants and surfactants. Maximum drug release was found in tablets containing 4% SSG with 4% SLS. So, bilayer tablets could be a potential dosage form for delivering paracetamol and aceclofenac.

4. Chitra Karthikeyini *et al*., [19] formulated and evaluated of the sustained release bilayer tablet of Aceclofenac sodium using superdisintegrant, sodium starch glycolate for the fast release layer and water immiscible polymers such as EudragitRL100 for the sustaining layer. The bilayer tablets of Aceclofenac sodium were prepared by direct compression method. Thedrug release from formulation was found to zero order kinetics. It was also found linear in Higuchi's plot which confirms that diffusion is one of the mechanism of drug release .In this studied formulation release the drug upto 24hrs.

5. Mujoriya R Z *et al*., [20] formulated and evaluated the bilayer tablet of Metoprolol Succinate Er and Amlodipine Besilate. The formulation were prepared by using different polymer (HPMC, Methocel, Carbapol) with different diluents (MCC, Cellulose Phosphate, Starch, Croscarmalose Sodium) and wet granulation method. it can be concluded that a stable bilayer tablet of Metoprolol succinate ER and Amlodipine besilate can be prepared by using HPMC K 15 M and carbomer as a polymer. It was found that the in vitro drug release of Metoprolol succinate ER was best explained by first order (r^2 =0. 9994), as the plots showed the highest linearity, followed by Higuchi's equation (r^2 = 0.9974) and zero-order (r^2 = 0.9471).

6. Nabin Karna *et al*., [21] designed and evaluated of novel sustained release bilayer tablets of Lornoxicam based on the combination of hydrophilic matrix formers and basic Ph modifiers. These tablets were prepared by wet granulation technique using basic pH modifiers like sodium bicarbonate & magnesium oxide to create basic micro-environmental pH inside &give a favorable acidic condition for tablets to release the drug. Different types and levels of hydrophilic matrixing agents, like HPMC K4 & HPMC K 15 were used to control the release of the drugs.

7. Chandrashekhar L. Bhingare *et al*., [22] formulated and evaluated the bilayer tablets of Atenolol and Hydochlorthiazide. The bilayered tablets gives biphasic drug release like loading dose of HCTZ and maintenance dose of Atenolol. The bilayered tablets are prepared using croscarmellose sodium as superdisintigrant for immediate released layer and different viscosity grades of hydrophilic polymers for sustained released layer. In this study, formulation made up from 10% CCS, and formulation made up from intra-granulation techniques and 30mg blend of polymers releases the total drug content at the end of the 60 minutes and 12 hrs respectively. The release data obtained from the dissolution study of bilayered tablets are analyzed with respect to zero order, first order,

Higuchi, Korsmeyer-Peppas models and release kinetic is fitted to Korsmeyer-peppasequation. The mechanism of drug release was regarded as anomalous diffusion of drug from matrix.

8. Brito Raj S *et al.,* [23] designed and evaluated the sustained release bilayer tablets of Metformin Hydrochloride and Metaprolol tartrate. Bilayer tablets were prepared by wet granulation technique using release retarding agents like HPMC K100, Eudragit S 100 for sustained release (SR) layer and super disintegrants like Crosspovidone, Sodium starch glycolate (SSG) for immediate release (IR) layer.All the formulations obey Zero order release kinetics and the mechanism of drug release was found to be non& fickian diffusion by fittingthe data to peppas equation.

9. Soham Shukla *et al.,* [24] formulated and evaluated the bilayer tablets of Telmisartan and Amlodipine Besilate both as immediate release layersusing full factorial design. Telmisartan layer (220 mg) and Amlodipine besilate layer (100 mg) were prepared by wet granulation method using various superdisintegrants and binders. Both Telmisartan and Amlodipine besilate layers were optimized using 3^2 factorial design. All formulations were evaluated for in vitro drug release analyzed according to various release kinetic models. Results shows that formulation optimized in Telmisartan layer which contained meglumine 7.5 % (16 mg) and crospovidone 5 % (11 mg) and formulation optimized in amlodipine besilate layer which contained starch paste 5 % (5 mg) and croscarmellose sodium 3% (3 mg).

10. Kotta Kranthi Kumar *et al*., [25]designed and characterized the sustained release bilayer tablets of Metformin hydrochloride and Gliclazide. Tablets were prepared by wet granulation method using HPMC as a release retardant. The best formula was selected by dissolution profile of Metformin hydrochloride was 101% and Gliclazide was 99% after 24 hours and similarity factor correlation studies 70.9% for Metformin hydrochloride and 67.2% for Gliclazide when compared with the innovater products.

11. Patel N *et al.,* [26] formulated and evaluated the bilayer tablets Telmisartan and Hydrochlorthiazide. The bilayer tablets were prepared by wet granulation technique. Telmisartan was converted to its sodium salt by dissolving in aqueous solution of sodium hydroxide to improve solubility and drug release. The tablets were formulated with high proportion of sodium starch glycolate showed that 101.11% and 99.89% respectively.

12. Mohamed Halith S *et al.*,[27] formulated and evaluated the bilayer tablets of Amlodipine besilate and Metprolol succinate In the formulation of immediate release sodium starch glycolate and pregelatinised starch were used as super disintegrant and was directly compressed. For sustained release portion HPMC polymers were used in granulation stage and also extragranularly. It was found that the optimized formulation showed 9.96%, 35.56%, 52.12%, 90.46% release for Metoprolol succinate in 1, 4, 8, 20 hours respectively. However, Amlodipine besilate released 98.28% at the end of 30 minutes. The kinetic studies of the formulations revealed that diffusion is the predominant mechanism of drug and release follows first order kinetics.

13. Mandeep Sharma*et al.*, [28] developed and Characterized the bilayer tablet Containing Metformin Hydrochloride in sustained release layer and Atorvastatin Calcium in immediate release layer. Bilayer tablets were prepared by wet granulation technique. The atorvastatin showed burst release whereas Metformin had sustained released. After 20 minutes, the Atorvastatin was completely released from formulation whereas for others drug release was less than 80 %. The steady state concentration of Metformin for all formulation was reached within 2-3h. The *in vitro* release studies data was quantified to determine the release mechanism, to fit various mathematical models and to determine which the best-fit model studied was zero order, first order and Higuchi model. The correlation coefficient was found to be equal to one for first order model. So, the developed tablets showed first order release behaviour.

14. Ch.Anil Kumar*et al.*, [29]formulated and evaluated the bilayer tablet of Metformin HCl and Glimepiride HCl of which Metformin HCl as sustained release and Glimepiride as immediate release layer. Sustained layer were prepared by wet granulation method using Eudragit's as polymers, immediate release layer were prepared by direct compression method using super disintegrants such as cross carmellose sodium and sodium starch glycollate. The *in vitro* release profile of drug from sustained release layer could be expressed by higuchi's equation as pilot show high linearity R^2=0.9911and diffusion was the dominant mechanism of drug release. The formulation having immediate release layer produces immediate effect 94.53 ± 0.30 within 45 minutes followed by sustained release effect 95.77 ± 0.37 up to 8 hours.

15. Jyotsna Godbole *et al.*,[30] formulated and evaluated the bilayer matrix tablets containing Acarbose as immediate release component using sodium starch glycolate and cross carmillose sodium as super disintegrates and Metformin hydrochloride (HCl) for sustained release by using hydroxyl propyl methyl cellulose (HPMC K 4M), (HPMC K 100) and sodium carboxyl methyl cellulose (SCMC) as the matrix forming polymer and PVPK-30 as binder. These release the drug by both as well as diffusion controlled mechanisms the half life of metformin HCl is 6.2 hrs, so an attempt was made in the direction of preparation and optimization of a combination of sustained release and immediate release in a single tablet. Tablets were prepared by wet granulation and direct compression method. The final preparation showed release of drug up to 96.75 in 8hours.

16. Rama *et al.*, [31] formulated and evaluated the bilayer tablets of two incompatible drugs Amlodipine besilate and Losartan potassium. Losartan potassium was prepared by wet granulation and Amlodipine besilate by direct compression. Super disintegrants like crospovidone, sodium starch glycolate were used in all formulation. The dissolution studies showed the drug release 84.02% for Amlodipine besilate and 90.08% for Losartan potassium in 30 minutes was selected as optimized formulation.

17. Margret chandira R *et al.*, [32] formulated and evaluated the bilayer floating tablets of Metformin Hydrochloride. The tablets were prepared by direct compression technique by using HPMC as release retardant, sodium bicarbonate as gas generating agent to reduce floating lag time. The in vitro drug release followed zero order kinetics and drug release was found to be diffusion controlled.

18. Ajit Kulkarni *et al.*,[33] formulated and evaluated the bilayer regioselective floating tablets of Atenolol and Lovastatin to give immediate release of Lovastatin and sustained release of Atenolol.The immediate release layer comprised sodium starch glycollate as a super disintegrant and the sustained release layer comprised HPMC K100M and xanthan gum as the release retarding polymers. Sodium bicarbonate was used as a gas generating agent. Direct compression method was used for formulation of the bilayer tablets. All formulations floated for more than 12 h. More than 90% of Lovastatin was released within 30 min. HPMC K100M and xanthan gum sustained retarded the release of Atenolol from the controlled release layer for 12 h. Diffusion exponents (n) were determined for all the formulations (0.53-0.59). The release of Atenolol was found to follow a mixed pattern of

Korsmeyer-Peppas, Hixson-Crowell and zero order release models. The optimized formulation was found to be buoyant for 8 h in stomach.

REVIEW LITEATURE FOR LISINOPRIL

19. Rajeshree Panigrahi *et al.,* [34] formulated and evaluated the fast dissolving tablet of Lisinopril. All the superdisintegrants such as crosscarmellose, crosspovidone, sodium starch glycolate were maintained in different concentrations in all the formulations. Microcrystalline cellulose was used as diluents and also as a superdisintegrant.*In vitro* drug release showed that formula crosspovidone and sodium starch glycolate had better % drug release as compare to other formulations.

20. Ashish Jain *et al.,* [35] formulated and evaluated the comparative release study of Lisinopril from different topical vehicles. An in vitro diffusion cell experiment was designed to reveal the rate of release of Lisinopril from three different topical vehicles: (i) an oil-in-water cream; (ii) a gel; and (iii) an ointment. Ointment base showed considerably higher drug release than other vehicles.

21. Basawaraj S.Patil *et al.,* [36] prepared and evaluated an oral pulsatile drug delivery system based on a press coated tablet. The core containing Lisinopril as a bioactive compound was prepared by direct compression method. The coating materials consisted of hydrophobic polymer of ethyl cellulose and hydrophilic materials (HPMC 15 CPS) were used in different concentration.

22. Anand Padole *et al.,* [37] formulated and evaluated the Buccal tablets of lisinopril by direct compression method using different hydrophilic polymers such as hydroxypropyl methylcellulose, sodium carboxy methylcellulose and Carbopol. Drug release mechanism was determined by plotting release data to Higuchi and Korsmeyer-Peppas model. According to this model the drug releases from theses tablets may be controlled by diffusion.

23. Pandey Shivanand *et al.,* [38] formulated and evaluated the taste masked fast disintegrating tablets of Lisinopril. It was concluded that beta cyclodextrins were useful for masking the taste as well as enhancing the solubility of the drug. Superdisintegrants were helpful in formulation of the Fast dissolving tablets. crosscarmellose Sodium is suitable for this formulation.

24. Shamsheer Ahmad S *et al.,* [39] formulated and Evaluated of Lisinopril Dihydrate Transdermal Proniosomal Gels and prepared by coacervation phase separation method. It was observed that the gel formulations showed good spreadability and viscosity. Determination of vesicle size was found to be 20.10-26.23µm.All formulations showed zero order drug release by diffusion mechanism.It showed that Lisinopril dihydrate proniosomal gel containing lecithin, cholesterol and in combination of surfactants like span 20, 40, 60,80 sustained release of drug over a period of 24 hrs.

25. Malpani Amol *et al.,* [40] formulated the Lisinopril dihydrate and studied the effect of extend of granulation on response variables. Lisinopril dihydrate tablet evaluation parameters like particle size distribution as well as drug release by changing the granulation time during formulation process. Mixing time, compression force and other can also some important variables which can be considered, depend upon formulation and excipients.

26. Manickam Balamurugan[41]formulated and evaluated the chitosan based bioadhesive transdermal drug delivery systems of lisinopril for prolonged drug delivery. It was prepared by solvent evaporation technique with different concentrations of chitosan without any penetration enhancers. *In-vitro* permeation studies were performed in cadaver skin and rat skin by using modified Franz diffusion cells. The results followed Higuchi kinetics (R^2=0.98), and the mechanism of release was diffusion mediated.

27. Izhar Kasid *et al.,* [42] developed and evaluated the bilayer tablets of lisinopril and Gliclazide. Both were prepared by direct compression technique. Lisinopril was formulated as fast dissolving layer using sodium starch glycolate, croscarmellose sodium as superdisintegrants. The optimized lisinopril fast dissolving layer (L-6) with highest in vitro release of 99.73% was selected. Gliclazide was formulated as sustained release layer using different polymer matrix like hydroxyethylcellulose, hydroxypropylcellulose, and ethylcellulose and evaluated for physical parameter along with *in vitro* release studies. The optimized sustained release layers (G-5) which extend the gliclazide release more than 8hrs was selected. The in vivo antidiabetic activity suggested that lisinopril potentiate hypoglycemic effect of gliclazide and blood glucose level was constantly maintained upto 24h.

REVIEW LITERATURE FOR GLIPIZIDE

28. Chakraborty Manas *et al*., [43] prepared Glipizide sustained release and immediate release bilayer matrix tablet by different concentration of Hydroxypropyl methylcellulose and Ethyl Cellulose to control the release pattern. The sustained release layer of Glipizide was prepared by using different grades of HPMC like, HPMC K-100, HPMC K-50 and Ethyl Cellulose along with other excipients bywet granulation technique. The immediate release layer of Glipizide was prepared by Lactose and Sodium starch glycolate by wet granulation Method. The release rate of Glipizide in immediate release layer was studied for 1h in pH 7.4 phosphate buffer media and that of Glipizide in sustained release layer was studied for 10 h in pH 7.4 phosphate buffer media. The dissolution release showed that showed good release behaviour 91.92% of drug is released over 10 hours and r^2 value is 0.977 in zero-order kinetics.

29. N.G.Raghavendra Rao*et al.,*[44] formulated and evaluated the controlled release zero order release Glipizide bilayer matrix tablet using different grades of natural and synthetic polymers such as xanthan gum, guar gum, karaya gum and hydroxyl methyl cellulose as novel release modifiers. The tablets were prepared by wet granulation method. The in vitro release study was performed in phosphate buffer pH 7.4 upto 12hours. The release data were fit into different kinetics model (zero order, fist order and korsemeyer-peppas powers law equation).

30. Hitendra S Mahajan *et al*., [45] formulated and evaluated the immediate release Glipizide liquidsolid tablets using Avicel PH-102 and Aerosil 200 as a carrier and coating material respectively to increase the dissolution rate of poorly soluble Glipizide. Gellan gum also used as a disintegrant. The results obtained shows that all Glipizide liquidsolid tablets exhibits higher dissolution rate than marketd tablets. Dissolution rate increases with increasing concentration of liquid vehicles and maximum drug release achieved by formulation containing polyethylene glycol 400 as a liquid vehicle.

31. BC Behera *et al*., [46] formulated and evaluated the microencapsulated Glipizide produced by the emulsion-solvent evaporation method. Microspheres were prepared using polymethacrylate polymers (Eudragit® RS 100 and RL 100) by solvent evaporation method and characterized for their micromeritic properties and drug loading, as well as by Fourier transform infrared spectroscopy (FTIR) and scanning electron microscopy. *In vitro* release studies were performed in phosphate buffer (pH 7.4). The resulting microspheres obtained

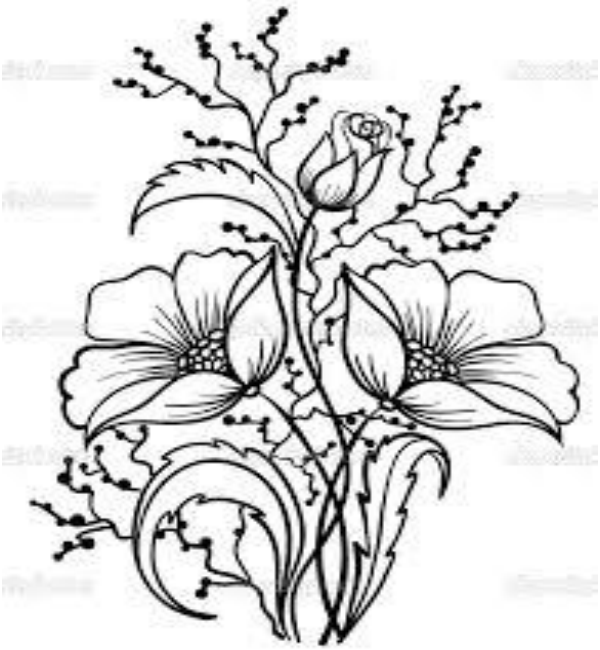
by solvent evaporation method were white and free flowing in nature. The mean particle sizeof microspheres ranged from 420 - 660 µ m and the encapsulation efficiencies ranged from 40.27 - 86.67 %.The mechanism of drug release from the microspheres was found to be non-Fickian type.

32. Bhavani Boddeda *et al.*,[47] formulated and evaluated the sustained release tablet formulation of glipizide by employing two hydrophobic polymers (ethyl cellulose and ethylene vinyl acetate copolymer) and two natural hydrophilic gum resins olibanum resin and colophony). Different batches of glipizide sustained release tablets were prepared by using lactose and dicalcium phosphate as diluents by wet granulation technique.The independent model method, Lin Ju and Liaw's difference factor ($f1$) and similarity factor ($f2$) were used to compare various dissolution profiles. The kinetics of drug release was best explained by Korsmeyer and peppas model and the mechanism of drug release from these tablets was by non-fickian diffusion mechanism.

33. Jinal Patel *et al.*,[48]formulated and evaluated the floating tablets of Glipizide were prepared by using different polymers like HPMC K100M, sodium alginate, Carbopol 940, and PVP K30 by effervescent technique. Sodium bicarbonate and citric acid were incorporated as a gas generating agent. Floating tablets containing glipizide were prepared by direct compression technique. All the prepared batches showed good *in vitro* buoyancy. The tablet swelled radially and axially during in vitro buoyancy studies. The dissolution release study observed that the tablet remained buoyant for 16-24 hours.

34. M Sivabalan *et al.*, [49] formulated and evaluated hydrodynamically balanced controlled drug delivery system of Glipizide.The tablets were prepared by direct compression method by using various polymerslike HPMC, MC and EC. The *in-vitro* release was found to be in the range of 59.25% to 79.50%.

35. J. L. Ramabargavi *et al.*, [50] formulated and evaluated the floating matrix tablets of Glipizide were prepared by Effervescent floating technique. The formulations were prepared by polymers HPMC 5cps and carbopol 940 used for matrix system, and incorporating $NaHCO_3$ into tablets. Tablets were formulated with different ratios of HPMC 5cps and carbopol 940 individually and combination of polymers.Different kinetic models were applied to optimized formulation the 'n' value is 0.333, r^2 value is 0.918 indicating Fickian Diffusion and first order release.



Aim & Plan of work

3. AIM AND PLAN OF WORK

AIM OF THE PROJECT WORK

- To provide effective, safe and stable pharmaceutical oral formulation containing antihypertensive drug Lisinopril as immediate release layer and oral antidiabetic drug Glipizide as sustained release layer for effective treatment of diabetes along with diabetic hypertension and nephropathy.
- To optimize immediate release tablets of Lisinopril by wet granulation method using various concentration of sodium starch glycolate as super disintegrant.
- To optimize sustained release tablets of Glipizide by wet granulation method using ethyl cellulose and swellable polymer HPMC K100M in different ratios.
- To formulate and evaluate the bi-layer tablets from the optimized batches of immediate release and sustained release formulations.

PLAN OF WORK

- Preformulation studies
    - Raw material analysis
    - Physical and chemical compatibility studies
- Construction of calibration curve
- Precompression studies of the drug, blend and Immediate release granules
    - Bulk density
    - Tapped density
    - Angle of repose
    - Carr's index
    - Hausner's ratio
- Formulation of Lisinopril immediate release(IR) tablets
- Post compression studies of Immediate release tablets for physical parameters like
    - Uniformity of weight
    - Physical appearance
    - Thickness, hardness and diameter
    - Friability
    - Determination of drug content of IR tablets
    - Disintegration studies of IR tablets

- Evaluation of *in vitro* dissolution study of IR tablets

- Precompression studies of the drug, blend and SR granules
  - Bulk density
  - Tapped density
  - Angle of repose
  - Carr's index
  - Hausner's ratio
- Formulation of sustained release (SR) tablets
- Post compression study of SR tablets for physical parameters like
  - Uniformity of weight
  - Physical appearance
  - Thickness & hardness
  - Length & diameter
  - Friability
  - Determination of drug content of SR tablets
  - Evaluation of *in vitro* dissolution study of SR tablets
- Formulation of bilayer tablets from the optimized batches of IR and SR layer
- Post compression study of bilayer tablets for physical parameters like
  - Uniformity of weight
  - Physical appearance
  - Thickness & hardness
  - Length & diameter
  - Friability
  - Determination of drug content by simultaneous equation method
  - Evaluation of *in vitro* dissolution study of bilayer tablets by simultaneous equation method
  - Evaluation of release kinetics of optimized bilayer formulation
  - Determination of stability of bilayer tablets as per ICH guidelines

Rationale of the Study

4. RATIONALE OF THE STUDY

RATIONALE FOR SELECTION OF LISINOPRIL

Lisinopril is the Lys analog of enalaprilat; unlike Enalapril, Lisinopril itself is active. Lisinopril is slightly more potent than enalaprilat. Lisinopril is absorbed slowly, variably, and incompletely (about 30%) after oral administration.

The RAS is involved in a wide range of adverse effects that contribute to metabolic diseases. ACE‑I are effective as antihypertensive agents, have utility in prevention of cardiac remodeling following myocardial infarct (MI), inhibition of heart and kidney disease, prevention of diabetes, and their use has even been associated with decreased mortality in patients hospitalized with community‑acquired pneumonia.ACE‑I therapy is now commonly prescribed to diabetic patients and has been associated with a lower likelihood of other complications including a history of cancer and peptic ulcers. Also, clinical studies have detected inhibition of diabetic retinopathy by ACE‑I. Lisinopril in Insulin Dependent Diabetes Study Group investigated the effect of the ACE‑I, Lisinopril, on retinopathy in normotensive type I diabetic patients. They found a 50% reduction in the progression of retinopathy in lisinopril treated subjects compared to controls.

National guidelines recommend ACE‑I therapy in patients with diabetes who also have hypertension and/or proteinuria to retard the progression of renal damage. One of the main characteristics of essential hypertension is nephrosclerosis, the first clinical sign of which is protein in the urine. Proteinuria is the main predictor of cardiovascular disease in patients with type 2 diabetes as well as progressive renal disease in type 1 diabetes and in patients with overt diabetic nephropathy.

RATIONALE FOR SELECTION OF GLIPIZIDE

Glipizide is a second generation sulfonylureas, an oral hypoglycemic agent for the management of non-insulin dependent diabetes mellitus.The half life of Glipizide is 2-5 hours;hence it is a suitable candidate for the design of sustained release drug delivery system.On a weigth basis, Glipizide is 100 times more potent than Tolbutamide. It has more rapid onset of effect than glyburide and a shorter duration of action.

Glipizide reduces blood glucose by stimulating insulin secretion and altering insulin sensitivity, the drug causes a sustained increase in glucose stimulated insulin secretion in most patients during prolonged therapy.

It improves glucose utilization not only by promoting pancreatic insulin release but also by enhancing extra pancreatic availability of insulin and the number of insulin receptors.By using sustained release dosage form the therapeutically effective concentration can be maintained for longer time than the conventional dosage form.

By the use of sustained release dosage form, saw tooth kinetics of blood levels associated with conventional multidosage form can be eliminated and also incident of the local and systemic adverse effects can be reduced.

By using the sustained release dosage form Glipizide has minimal side effects and safer drug to diabetes.

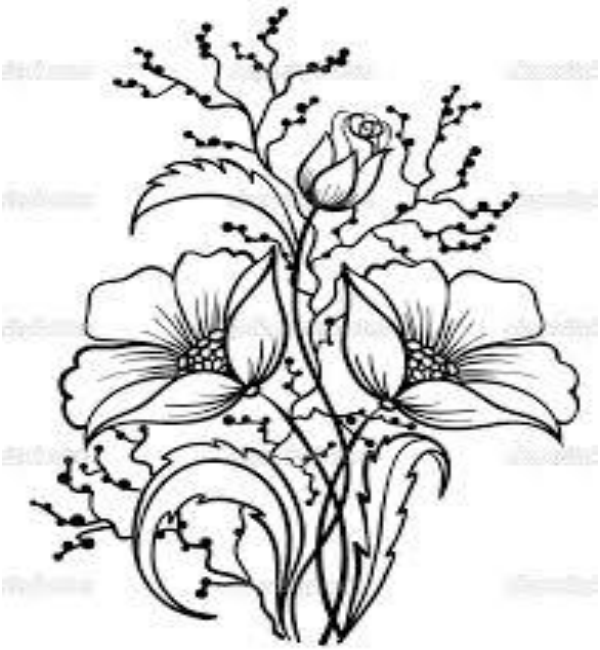
RATIONALE FOR SELECTION OF LISINOPRIL AND GLIPIZIDE FOR FORMULATING BILAYER TABLETS

Most of the patients with type 2 diabetes have insulin resistance is related to hypertension and frequently is a comorbidity. Patients with diabetes are more likely to be hypertensive than nondiabetics, and hypertension is linked with cardiovascular disease, stroke, progression of renal disease, and other complications. The cardiovascular morbidity and mortality related to diabetes are very high.

Proteinuria is the main predictor of cardiovascular disease in patients with type 2 diabetes as well as progressive renal disease in type 1 diabetes and in patients with overt diabetic nephropathy. These complications are reduced by bilayer tablet.

Lisinopril potentiate hypoglycemic effect of Glipizide and blood glucose level was constantly maintained upto 24 h. Hence bilayer tablets of Lisinopril and Glipizide as fast and sustained release combination could be used to improve patient compliance towards the effective management of diabetes along with diabetic hypertension and nephropathy.

In order to reduce the polytherapy too monotherapy in patients with hypertension and type 2 diabetes and improve the patient compliance when two drugs are used in a single dosage form rather than taking individual.



Profiles

5. DISEASE PROFILE

DIABETES MELLITUS[51, 52]

Diabetes mellitus is a chronic disorder characterized by impaired metabolism of glucose. Diabetes mellitus is a group of disorders involving distinct pathogenic mechanisms with hyperglycemia as the common denominator. Regardless of the cause, the disease is associated with insulin deficiency, which may be total, partial or relative when viewed in respect of co-existing insulin resistance.

Diabetes mellitus has reached epidemic proportions and affects more than 170million individuals worldwide. In more developed societies, the prevalence of diabetes mellitus has reached about 6% and even more alarmingly, among obese white adolescents 4% had diabetes and 25% had abnormal glucose tolerance. Some 90% of diabetic individuals have Type-2 (Non-Insulin-dependent) diabetes mellitus, and within this category no more than10% can be accounted for monogenic forms such as maturity-onset diabetes of the young and mitochondrial diabetes or late-onset autoimmune diabetes of the adult, which is actually late-onset Type 1 diabetes. Thus, most diabetes in the world is accounted for by "common" Type 2 diabetes, which has a multifactorial pathogenesis caused by alterations in several gene products.

CAUSES

Insulin is a hormone produced by the pancreas to control blood sugar. Diabetes can be caused by deficiency of insulin, resistance to insulin or both. People with diabetes have high blood sugar. This is because:

- Their pancreas does not make enough insulin
- Their muscle, fat, and liver cells do not respond to insulin due to insulin resistance.

Classification of Diabetes Mellitus[53, 54, 55]

1. Type 1 diabetes (beta cell destruction, usually leading to absolute insulin deficiency)

a) Immune Mediated

b) Idiopathic

2. Type 2 diabetes (may range from predominantly insulin resistance with relative insulin deficiency to a predominantly secretary defect with relative insulin resistance).

3. Other Specific Types

a. Genetic defects of beta cell function and insulin action

b. Disease of the exocrine pancreas

c. Endocrinopathies

d. Drug induced

e. Infections

f. Gestational Diabetes

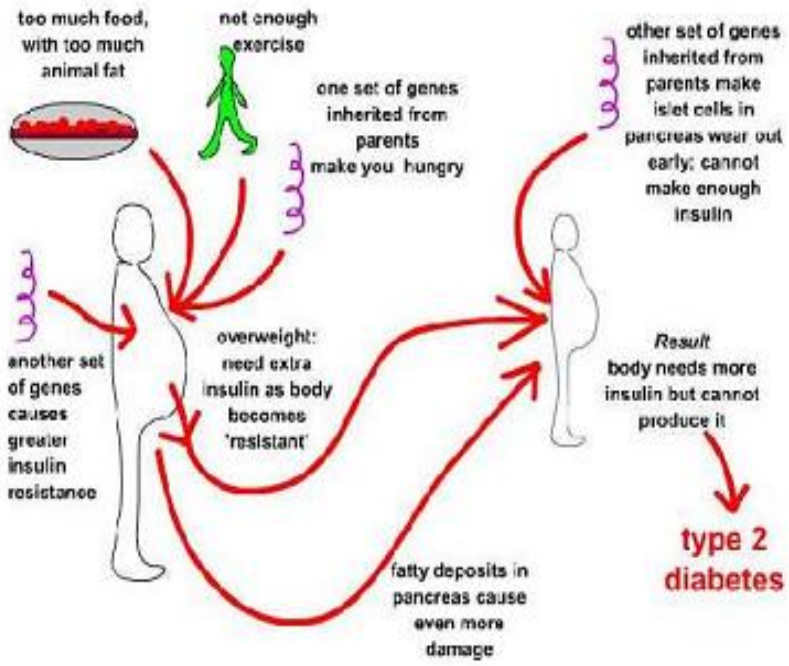


Fig 9: Metabolic causes of Type 2 diabetes mellitus

Symptoms of Diabetes Mellitus

The classical symptoms of diabetes mellitus are:

- Polydipsia (Increased intake of water due to increased thirst)
- Polyuria (Increased formation of urine)
- Polyphagia (Increased ingestion of food).

Diagnosis of Diabetes Mellitus

Two kinds of blood estimations are done to estimate the normal plasma glucose levels. The first one is known as Random Plasma Glucose (RPG) in which a sample is drawn at any "random" time during the day without consideration to the "fed" state of the patient. The others are samples known as Fasting Plasma Glucose (FPG) followed by Post - prandial Plasma Glucose (PPG). The patient is advised not to eat anything after dinner till the blood sample for FPG is withdrawn the next morning. There are three ways to diagnose diabetes each must be confirmed on a subsequent day, by any one of the three methods.

1. FPG> 126mg/dl (0.7 mmol/l), fasting is defined as no caloric intake for at least8hours.

2. 2-h PPG> 200 mg/dl (11.1mmol/1) during an Oral glucose Tolerance Test (OGTT).

The Expert Committee recognizes an intermediate group of subjects whose (FPG>110 mg/dl (6.1 mmol/l) but < 126mg/d; (7.0 mmol/l) or 2-h values in the OGTT of >140 mg/dl (7.8mmol/l)but <200 mg/dl (11.1mmol/l). Thus, the categories of FPG values are as follows,

- FPG< 110 mg/dl (6.1 mmol/l) = normal fasting glucose
- FPG> 110 mg/dl (6.1 mmol/l) and < mg/dl (7.0mmol/l) = FPG
- FPG> 126 mg/dl (7.0 mg/dl) = provisional diagnosis of diabetes (the diagnosis must be confirmed, as described above)

COMPLICATIONS OF DIABETES MELLITUS

Acute complications	Chronic complications
1. Infections 2. Diabetic ketoacidosis 3. Hyperosmolar coma	Micro-vascular 1. Retinopathy 2. Neuropathy 3. Nephropathy Macro-vascular 1. Coronary artery disease 2. Stroke 3. Peripheral vascular disease 4. Non healing ulcer

Abnormalities in Beta Cell Function in Type 2 Diabetes

Glucose homeostasis that requires a balance between glucose production by the liver and glucose utilization by insulin–dependent tissues (such as fat and muscle) and insulin–independent tissues (such as the brain)., is regulated by insulin production in beta cells and glucagon production in alpha cells of the pancreatic islets. In Type 2diabetes, there are defects in both peripheral tissue responses to insulin and beta cells response to glucose. In Type 2 diabetes there are two defects: reduction in the ability of peripheral tissues to respond to insulin (insulin resistance) and a relative insulin deficiency resulting from an inability of the beta cells to compensate for this resistance.

Biochemical Changes Associated With Insulin Deficiency

Insulin deficiency depresses glucose transport into the cell and glycogen synthesis in the muscle. At the same time there is an increase in protein breakdown. Insulin lack leads not only to under utilization of glucose at the cellular level but also promotes gluconeogenesis. All this lead to hyperglycemia which is associated with polys. Low insulin levels leads to increased hormone sensitive lipase activity in adipose tissues cells. Long chain fatty acids released are broken down to large quantities of acetyl coenzyme–A, which instead of being burnt by the tricarboxylatedacid cycle is diverted to the formation of acetoacetate. Acetoacetate is decarboxylated to give acetone or reduced to from beta hydroxybutrate. Acetone, acetoacetate and betahydroxy butyric acid are collectively known as ketone bodies. Ketone bodies, being volatile are excreted in the breath and in the urine.

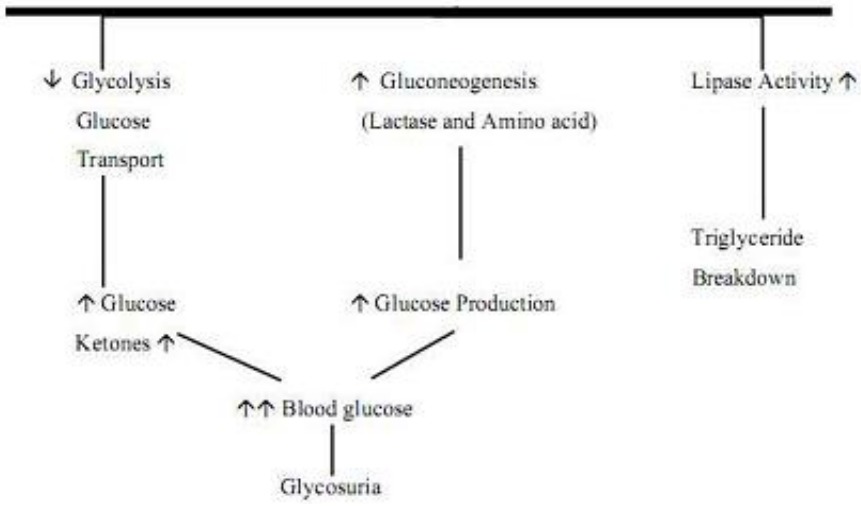


Fig 10: Insulin deficiency

Insulin Resistance

Insulin resistance is a state in which normal amount of Insulin produces a subnormal amount of Insulin response. There is an impaired biological response to insulin by one or more of its target tissues leading to reduced glucose disposal. Defects in binding of insulin to its receptors due to the reduction in their number or affinity would result in Insulin resistance. Clinically insulin resistance stage falls in two categories.

- Decreased sensitivity: where normal response can be obtained with supramaximal insulin levels.
- Decreased responsiveness: Even massive doses of insulin cannot produce a normal level or response. There is an increase in Hepatic glucose output (which contributes primarily to fasting hyperglycemia) and reduction in peripheral glucose utilization. There is also elevation of plasma FFA (freefatty acids) resulting from activation of lipolysis.

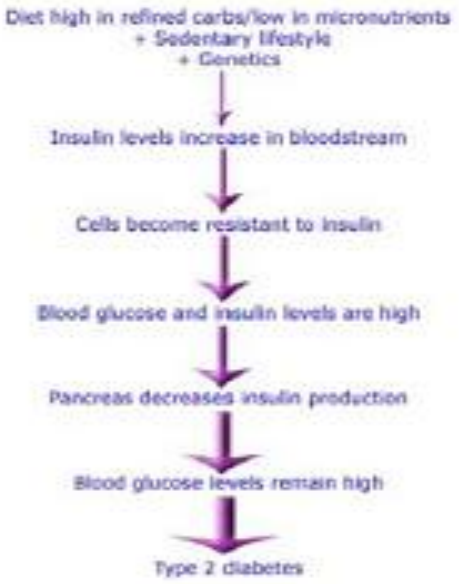


Fig 11: Progression insulin resistance towards type 2 Diabetes mellitus

Management of Type 1 Diabetes

Insulin therapy

Numerous preparations of Insulin are available to cater to the diverse requirements of different patients. The preparations differ in their:

1. Onset of action

2. Duration of action

3. Purity (Conventional, Purified)

4. Species of origin (Human, Pork, Bovine–in order of preference)

Based on their onset and duration of actions, the insulin may be divided into:

a) Rapid acting

Insulin Injection (Regular, Crystalline Zinc)

b) Intermediate Acting

Isophane (NPH) 70%, Regular Insulin 30%, Isophane (NPH) Insulin Suspension

c) Long Acting

Extended Insulin zinc suspension (Ultralente): The intermediate acting Isophane(NPH) insulins are conjugated to Protamine, large-protein molecule which delays absorption thereby prolonging the duration of action. It is a mixture of 70% ultralenteand30% semi-lente. The long-acting Ultralente zinc-insulin suspension has a large particle size and crystalline form which retards the rate of absorption and thus prolongs the duration of action.

Management of Type 2 Diabetes

The treatment of patients with Type 2 diabetes goes beyond normalizing blood glucose levels; therapy is also directed toward alleviating symptoms, minimizing acute complications (e.g., hypoglycemia), increasing the patient's sense of well-being and quality of life, minimizing chronic complications such as nephropathy, neuropathy, and macrovascular and microvascular disease. The initial therapy in Type2 diabetes is nutrition and exercise, with a program designed to encourage weight loss. The decision to use oral glucose- lowering agents generally takes place after atrial period of diet and exercise. To be maximally effective however, a nutritionally correct diet and regular exercise should support any pharmacologic intervention.

Among oral hypoglycemic agents the older groups that means sulfonylureas and biguanies are still extensively used. Several new drugs have appeared in the recent years which act through different mechanisms of action. Their use as monotherapy or in combination with other drugs will help to get a better glycemic control.

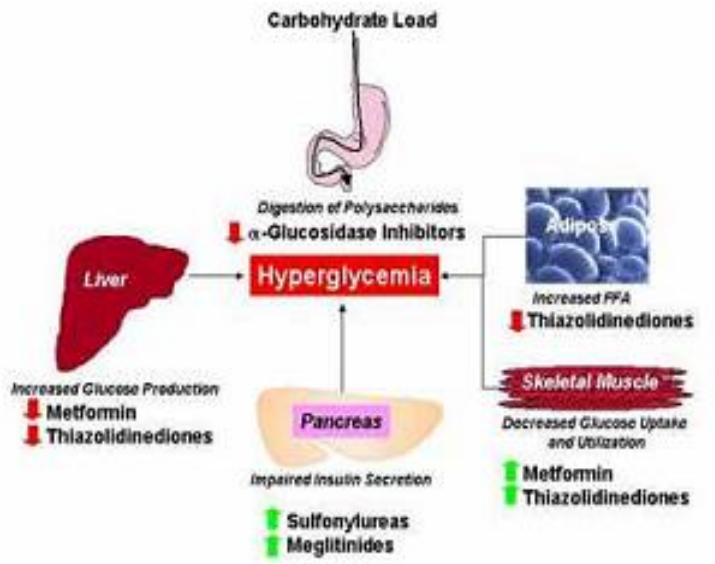


Fig 12: Mechanism of action oral hypoglycemic agents

Morbidity and Mortality of Type 2 Diabetes Mellitus

Diabetes mellitus (DM) is the main cause of mortality and morbidity in the developed world. The low compliance with the prescribed and self–administered treatments is well known to be a great problem in treating chronic disease such as in the case of DM. Patients with Type 2 diabetes are prone to both acute and long–term complications. Long–term diabetic complications are related to the effects of chronic hyperglycemia on the microvasculature.

Diabetes–related complications may have grim outcomes: Diabetes is the leading cause of blindness in adults, of end –stage renal disease, and of non trauma necessitated amputations. Retinopathy is seen is 12% to 44% of patients with Type 2diabetes 10 years after diagnosis and is present at the time of diagnosis in 10% to 20%of patients. Nephropathy leading to end–stage renal failure occurs in 4% to 20% of patients with Type 2 diabetes. It is well established that Type 2 diabetes is an independent risk–factor for cardiovascular disease–Type 2 diabetes patients have a2-to 3-fold increase in morbidity and mortality related to coronary artery disease, as well as an increased incidence of peripheral vascular disease. In

one study examining the prevalence of complications in patients with Type 2 diabetes, 48% had coronary artery disease, 56% were hypertensive, 15% exhibited signs of cerebrovascular disease and 35% has peripheral artery disease .The complexity of Type 2 diabetes and associated co-morbidities will continue to present a formidable challenge for successful pharmacological treatment.

Perspectives

Despite the magnitude of the disease, the choice of oral anti hyperglycemic drugs for Type 2 diabetes was limited to sulfonylureas for over 40 years. The last 11years have witnessed the introduction of four new classes of oral anti hyperglycemic therapies. Each possesses a distinct mechanism of action, which enables their use independently and, in some cases, as combination therapy. Combination drug therapy is not new. Combinations were frowned upon in much of the 20thcentury because of the prevailing philosophy was to seek a single "silver bullet" to treat a disease rather than prescribe multicomponent formulations to be dispensed by Pharmacist (or)Physicians. Current guidelines for combination therapy advice the use of agents with differing and complementary mechanism of action which mainly arises in the treatment of diabetes in order to maximize therapeutic activity and reduce toxicity. This is important since most patients with Type 2 diabetes will require combination therapy to reach an acceptable level of glycemic control.

Several types of oral diabetes medications, which work to lower blood glucose:

Sulphonylureas: This family of medications includes Gliclazide, Glimepride and Glipizide. These medications are widely recommended for type 2 diabetes and work by stimulating the pancreas to release insulin.

Biguanides: These medications include Metformin and work to improve insulin sensitivity and to reduce the glucose produced by liver.

Acarbose: This type of medication prolongs the absorption of carbohydrates after a meal. For these pills to work, they must be taken with or after a meal.

Thiazolidinediones: This family of medications includes Pioglitazone and Rosiglitazone and they work to improve the insulin sensitivity.

Meglitinides: This family of medications includes Repaglinide and Nateglinide. They lower postprandial (after meal) glucose levels by stimulating the pancreas to release insulin.

Dipeptidyl peptidase- 4 inhibitors: This family of medications includes Sitagliptin and Saxagliptin. They help to improve the insulin release from the pancreas and decrease liver release of glucose.

GLP -1 analog: This class of medications includes Liraglutide, which is a synthetic form of the hormone GLP-1. It helps the body release insulin when blood sugar levels are high, and also reduces the release of sugar from the liver. It is taken as a daily injection under the skin.

Hypertension[53]

Hypertension is defined as sustained elevation of systemic arterial blood pressure. Blood pressure is the force, which the blood put against the walls of arteries as it flows through them. Arteries are the blood vessels that carry oxygenated blood from the heart to the body's tissue.

CLASSIFICATION[54, 55]

Primary hypertension

It is also called as essential or idiopathic hypertension, affects 90% to 95% of hypertensive individuals.

Secondary hypertension

It is caused by altered hemodynamics associated with primary disease, such as renal disease. Although many diseases causes secondary hypertension, this forms of hypertension, this forms of hypertension accounts of 5% to 8% of cases.

Isolated hypertension

It is elevated blood pressure accompanied by normal diastolic blood pressure (below 90mmHg). It is the manifestation of increased cardiac output or rigidity of aorta or both.

Risk factors

For primary hypertension

- Family history
- Advancing age
- Race (most common in blacks)
- Obesity
- Tobacco use
- High intake of sodium or saturated fat
- Excessive alcohol consumption
- Life style, stress

For secondary hypertension

- Excessive rennin
- Mineral deficiencies (calcium, potassium and magnesium)
- Diabetes mellitus
- Renal artery disease
- Brain tumor, head injury
- Cushing's syndrome
- Thyroid, pituitary o parathyroid dysfunction
- Hormonal contraceptive, cocaine, sympathetic stimulants, MAO inhibitors
- Pregnancy

PATHOPHYSIOLOGY

Arterial blood pressure is a product of total peripheral resistance and cardiac output. Cardiac output is increased by conditions that increase heart rate or stroke volume or both. Peripheral resistance is increased by factors that increase blood viscosity or reduce the lumen size of vessels.

Several mechanisms may lead to hypertension, including

- Changes in the arteriolar bed causing increased peripheral vascular resistance.
- Abnormally increases tone in the sympathetic nervous system that originates in the vasomotor system centers, causing increased peripheral vascular resistance.

- Increased blood volume resulting from renal or hormonal dysfunction.
- Arteriolar thickening caused by genetic factors, leading to increased peripheral vascular resistance.
- Abnormal rennin release, resulting in the formation angiotensin II, which constricts the arteriole and increased blood volume.

Prolonged hypertension increases the workload of the heart as resistance to left ventricular ejection increases. To increase contractile force, the left ventricle hypertrophies, raising the oxygen demand and workload of the heart.

The pathophysiology of secondary hypertension is related to the diseases like, stroke, mycordial infarction, heat failure, arrhythmias, retinopathy, encephalopathy and renal failure.

SIGNS AND SYMPTOMS

- Generally produce no symptoms
- Occipital headache
- Epistaxis possibility due to vascular environment
- Bruits
- Dizziness, confusion, fatigue
- Blurry vision
- Nocturia
- Edema

DIAGNOSTIC TEST RESULTS

- Serial blood pressure measurements show elevation
- Urine analysis shows protein, casts, red blood cells or white blood cells suggesting renal disease, presence of catechlomines associated with pheochromocytoma or glucose, suggesting diabetes
- Blood chemistry reveals elevated blood urea nitrogen and serum creatinine levels suggestive of renal disease or hypokalaemia indicating adrenal dysfunction.
- Excretory urography may reveal renal atrophy, indicating chronic renal disease.
- Electrocardiography detects left ventricular hypertrophy or ischemia.
- Chest X-ray shows cardiomegaly.
- Echocardiography reveals left ventricular hypertrophy.

TREATMENT

- Lifestyle modification to reduce risk factors
- Diuretics
- Angiotensin converting enzyme inhibitors
- Alpha adrenergic receptor blockers
- Alpha adrenergic receptor agonists
- Bete adrenergic receptor blockers
- Treatment of underlying cause

Role of the Renin-Angiotensin [56, 57]

The Renin-Angiotensin System (RAS) is an important component for the homeostasis of blood flow. Renin is released from juxtaglomerular cells of the kidney in response to reduced renal perfusion pressure, reduced salt transport to the distal tubule, or increased renal sympathetic tone.

The action of renin on its liver-generated substrate, angiotensinogen, generates the inactive decapeptide, angiotensin I (Ang I), which is hydrolyzed by angiotensin-converting enzyme (ACE) to the octapeptide, angiotensin II(Ang II). ACE conversion of Ang I occurs primarily in the lungs, producing changes in Ang II levels that vary in accordance to plasma renin levels.

There is growing evidence that local systems in various tissues and organs are capable of generating Ang II including the adrenal gland, brain, heart, kidney, vasculature, adipose, gonads, pancreas, prostate, retina, and liver.

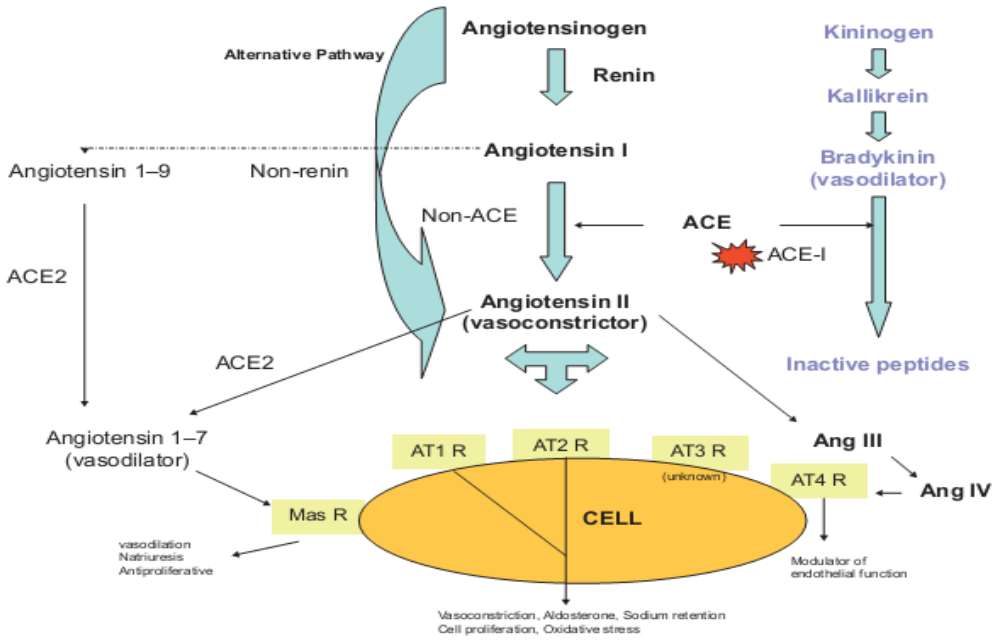


Fig 13: Schematic representation of Renin-Angiotensin cascade

Ang II is perhaps the most biologically active, triggering elevation in blood pressure by direct vasoconstriction, the stimulation of thirst by causing vasopressin release, and the induction of aldosterone production leading to water retention and facilitation of sympathetic activity.

Ang II has also been implicated in insulin resistance by inhibiting insulin receptor dependent PI3K signaling. Additionally, Ang II and can act on the AT1 receptor, thereby decreasing insulin-induced nitricoxide production and at the same time activating NADPH oxidase leading to enhanced production of other reactive oxygen radicals and enhancing inflammation. That hypertension is a common characteristic of insulin-resistant diabetes, with observed increases in tissue Ang II seen coupled with the inhibition of the vasodilator, nitricoxide, is not surprising.

Further, it has been shown that in diabetic patients, therapeutic inhibition of the RAS increased nitric oxide activity in renal endothelium, having a positive influence on renal function, and possibly cardiovascular function as well.

ACE-I Blockage and Diabetic Complications

Insulin resistance is related to hypertension and frequently is a comorbidity. Patients with diabetes are more likely to be hypertensive than nondiabetics, and hypertension is linked with cardiovascular disease, stroke, progression of renal disease, and other complications.

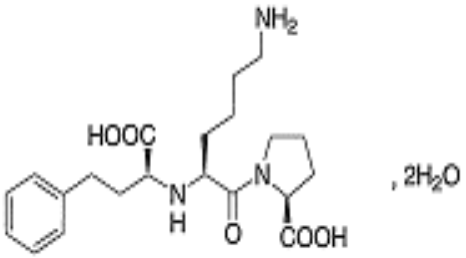
The cardiovascular morbidity and mortality related to diabetes are very high. The RAS is involved in a wide range of adverse effects that contribute to metabolic diseases. ACE‐I are effective as antihypertensive agents, have utility in prevention of cardiac remodeling following myocardial infarct (MI), inhibition of heart and kidney disease, prevention of diabetes, and their use has even been associated with decreased mortality in patients hospitalized with community‐acquired pneumonia.

Furthermore, evidence is starting to accumulate for further beneficial uses of these drugs in diabetic patients. In spite of the accumulating evidence on the benefits of ACE‐I therapy, there is an underuse of ACE‐I in patients with diabetes.

6. DRUG PROFILE[61, 62]

LISINOPRIL

Chemical structure :



Chemical name :(S)-1-[N^2-(1-carboxy-3-phenylpropyl)-L-lysyl]-L-proline dehydrate

Molecular formula : $C_{21}H_{31}N_3O_5$, $2H_2O$

Molecular weight : 441.5

Description : A white crystalline powder

Melting point : Melts between 146°C - 148° C

Solubility : Soluble in water. Very slightly soluble in ethanol(95 percent).

Loss on drying : Maximum 0.4 per cent, determined on 0.500g by drying in vacuo at 60° C

Sulphated ash : Not more than 0.1 %

Mechanism of action

- ACE-inhibitors are competitive inhibitors of angiotensin-converting enzyme (alsoknown as kininase II). ACE inhibitor administration results in significantly decreased plasma concentrations of angiotensin II and decreased plasma aldosterone concentrations (and increased concentrations of angiotensin I). Angiotensin

converting enzyme is also responsible for the degradation of bradykinin, a naturally occurring vasodilator.

- There is some evidence to show that ACE-inhibitors are responsible for the inhibition of this pathway leading to an accumulation of bradykinin. Bradykinin enhances the production of vasodilators, including endothelium derived relaxing factor (EDRF = NO = nitrogen monoxide) and prostaglandin (PG) E2 and I2.
- Recent studies show that bradykinin stimulates epoxyeicosatrienoic acid release. Epoxyeicosatrienoic acids are cytochrome P450 epoxygenase metabolites of arachidonic acid. They are synthesized by the vascular endothelium and open calcium-activated potassium channels, hyperpolarize the membrane, and relax vascular smooth muscle, resulting in vasodilation, independently of NO and PG production Cutaneous vasodilation results in an increased skin temperature and redness. Flushing therefore isan adverse reaction, which can be directly related to the pharmacological effect of many vasodilator drugs, including calcium antagonists and nitrates.

Pharmacokinetics

Absorption	: Approximately 25%, but widely variable between individuals (6 to 60%) in all doses tested (5-80 mg); absorption is Unaffected by food.
Bioavailability	: 25%
Half life	: Effective half life of accumulation following multiple dosing is 12 hours.
Plasma protein binding	: Lisinopril does not appear to be bound to serum proteins other than ACE.
Volume of distribution	: 31-36 liter
Metabolism	: Does not undergo metabolism, excreted unchanged in urine.
Excretion	: Lisinopril does not undergo metabolism and is excreted unchanged entirely in the urine.

Therapeutic indication : For the treatment of hypertension and symptomatic congestive heart failure. May be used in conjunction with thrombolytic agents, aspirinand/or β-blockers to improve survival in hemodynamically stable individuals following myocardial infarction. May be used to slow theprogression of renal disease in hypertensive patients with diabetes mellitus and microalbuminuria or overt nephropathy.

Routes and dosage : For oral dose (tablets): For congestive heart failure:Adults: 2.5 to 20 mg once a day.For Hypertension: Adults: 10 to 40 mg Once a day.

Contraindications and precautions

The ACE inhibitors are contraindicated in patients with:

■ Previous angioedema associated with ACE inhibitor therapy

■ Renal artery stenosis (bilateral or unilateral with a solitary functioning kidney)

■ Hypersensitivity to ACE inhibitors

ACE inhibitors should be used with caution in patients with:

■ Impaired renal function

■ Aortic valve stenosis or cardiac outflow obstruction

■ Hypovolemia or dehydration

■ Hemodialysis with high-flux polyacrylonitrile membranes

ACE inhibitors are ADEC pregnancy category D, and should be avoided in women who are likely to become pregnant. In the U.S., ACE inhibitors must be labelled with a "blackbox" warning concerning the risk of birth defects when taken during the second and third trimester.

Their use in the first trimester is also associated with a risk of major congenital malformations, particularly affecting the cardiovascular and central nervous systems.

Potassium supplementation should be used with caution and under medical supervision owing to the hyperkalemic effect of ACE inhibitors.

Adverse effects

Common adverse drug reactions include: hypotension, cough, hyperkalemia, headache, dizziness, fatigue, nausea, and renal impairment. Fein also suggests ACE inhibitors might increase inflammation-related pain, perhaps mediated by the buildup of bradykinin that accompanies ACE inhibition.

ACE inhibitors may cause hyperkalemia. Suppression of angiotensin II leads to a decrease in aldosterone levels. Since aldosterone is responsible for increasing the excretion of potassium, ACE inhibitors can cause retention of potassium. Some people, however, can continue to lose potassium while on an ACE inhibitor.

A severe rare allergic reaction can affect the bowel wall and secondarily cause abdominal pain. Some patients develop angioedema due to increased bradykinin levels. There appears to be a genetic predisposition toward this adverse effect in patients who degrade bradykinin more slowly than average.

In pregnant women, ACE inhibitors taken during the first trimester have been reported to cause major congenital malformations, stillbirths, and neonatal deaths. Commonly reported fetal abnormalities include hypotension, renal dysplasia, anuria/oliguria, oligohydramnios, intrauterine growth retardation, pulmonary hypoplasia, patent ductus arteriosus, and incomplete ossification of the skull.Overall, about half of newborns exposed to ACE inhibitors are adversely affected.

Drug interactions

1. Amiloride - Increased risk of hyperkalemia
2. Lithium - The ACE inhibitor increases serum levels of lithium
3. Spironolactone -Increased risk of hyperkalemia
4. Tizanidine - Increases the risk of hypotension with the ACE inhibitor
5. Spironolactone -Increased risk of hyperkalemia
6. Tobramycin -Increased risk of nephrotoxicity

Food interaction

- High salt intake may attenuate the antihypertensive effect of lisinopril.
- Lisinopril decreases the excretion of potassium. Salt substitutes containing potassium Increase the risk of hyperkalemia.
- Take without regard to meals.

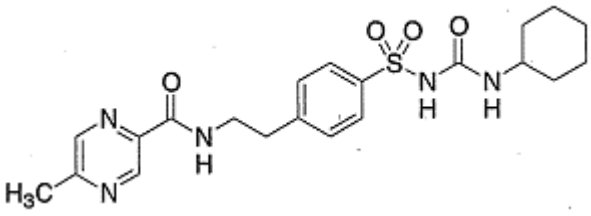
Combination with other drugs

Lisinopril + Hydrochlorthiazide

Lisinopril + Amlodipine

GLIPIZIDE[63, 64]

Chemical structure :



Chemical name : 1-cyclohexyl-3-[[4-[2-[[(5-methylpyrazine-2-yl)carbonyl]amino]ethyl]phenyl]sulphonyl]urea

Molecular formula : $C_{21}H_{27}N_5O_4S$

Molecular weight : 445.5

Description : A white or almost white, crystalline powder.

Solubility : Practically insoluble in water, very slightly soluble in methylene chloride and in acetone, practically insoluble inethanol (96 per cent). It dissolves in dilute solutions of alkali hydroxides.

Melting point : Melts between 208° C - 209° C

Loss on drying : Not more than 0.5 percent, determined on 1g by drying In an oven at 105° C.

Sulphated ash : Not more than 0.2 percent.

Mechanism of action :

Glipizide is a second generation sulfonylureas, an oral hypoglycaemic agent for the management of non-insulin dependent diabetes mellitus (type II diabetes). Glipizide has a more rapid onset of hypoglycaemic effect than Glyburide (Glibenclamide) and a shorter duration of action. Glipizide reduces blood glucose by stimulating insulin secretion and altering insulin sensitivity.

Sulfonylureas receptor on the pancreatic beta-cell inhibiting the adenosine triphosphate dependent potassium channel (K-ATP). Stabulization of potassium efflux causes depolarization and activation of the L-type calcium channel. Influx of calcium stimulates insulin secretion. The effect of sulfonylurea is similar to that of glucose at the cellular level; however, sulfonylureas only stimulates phase I (initial rapid peak) release of insulin and shows no effect on phase II (prolonged insulin release). When sulfonylurea treatment is initiated, insulin levels increase and plasma glucose levels gradually decrease. As the glucose levels decrease, insulin levels also decrease but still remain higher than pretreatment level.

Pharmacokinetics

Absorption : Gastrointestinal absorption is uniform, rapid, and Essentially complete.

Half life : 2-5 hours

Plasma protein binding : 98-99%, primarily to albumin.

Metabolism : Glipizide is metabolized by cytochrome P450 enzymes.

Excretion : The primary metabolites are inactive hydroxylation products and polar conjugates and are excreted mainly in the urine.

Therapeutic indication : Indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus.

Routes and dosage : Oral routes of administration – 2.5mg, 5mg and 10mg. The maximum recommended daily dose of Glipizide is 40mg per day.

Contraindication : Glipizide is contraindicated in pregnancy, lactation, renal insufficiency, impaired adrenocortical function, ketoacidosis.

Adverse effects :

1. Cardiovascular - Edema, syncope
2. Central nervous system - Anxiety, depression, dizziness, headache, insomnia
3. Dermatologic - Rash, urticaria, photosensitivity, pruritus
4. Endocrine & metabolic - Hypoglycemia, hyponatremia
5. Gastrointestinal - Anorexia, nausea, vomiting, diarrhea
6. Hematologic - Hemolytic anemia, bone marrow depression
7. Hepatic - Cholestatic jaundice, hepatic porphyria
8. Neuromuscular& skeletal - Arthralgia, leg cramps, myalgia, tremor
9. Ocular - Blurred vision
10. Renal - Diuretic effect

Drug interactions :

Atenolol - May decrease symptoms of hypoglycemia.

Rifampin - May decrease the effect of Glipizide.

Chloamphenicol - May increase the effect of Glipizide.

Clofibrate - May increase the effect of Glipizide.

Food Interactions

1. Avoid alcohol.
2. Avoid sugar and sugary food.
3. Take 30-60 minutes before breakfast.

Combination with the other drugs

Glipizide and Metformin

7. EXCIPIENTS PROFILES

PHARMACEUTICAL EXCIPIENTS

Pharmaceutical excipients are substances, other than the pharmacologically active drug or prodrug, which are included in the manufacturing process or contained in the finished pharmaceutical product dosage form. Excipients provide enhanced functionality to the pharmaceuticals, aid the innovations in the drug development and help improve patent life as well. Excipients make the products more functional at a lower cost, a benefit much desired by the pharmaceutical industry that is inundated with pressures to reduce costs.

Excipients play a wide variety of functional roles in pharmaceutical dosge forms. Including,

- Modulating the solubility and bioavailability of active pharmaceutical ingredients.
- Increasing the stability of active ingredients in dosage forms.
- Helping active ingredients maintain preferred polymorphic forms or conformations.
- Maintaining the pH and/or osmolarity of liquid formulations.
- Acting as antioxidents, emulsifying agents, aerosol propellants, tablet binders and tablet disintegrants.
- Preventing aggregation or dissertation (e.g of protein and polysaccharides actives).
- Modulating immunogenic responses of active ingredients (e.g adjunts).

SODIUM STARCH GLYCOLATE[65]

1. Non proprietary names

BP: Sodium Starch Glycolate, PhEur: Sodium Starch Glycolate, USP-NF: Sodium Starch Glycolate.

2. Synonyms

Carboxy methyl starch, sodium salt; carboxy methyl amylum natricum; Explosol: Explotab; Glycolys; Primojel; starch methyl ether, sodium salt; Tablo; Vivastar P.

3. Chemical name

Sodium carboxy methyl starch

4. Functional category

Tablet and capsule disintegrant

5. Description

Sodium starch glycolate is a white or almost white free-flowing very hygroscopic powder.

6. Solubility

Practically insoluble in methylene chloride. It gives a translucent susupension in water.

7. Applications

Sodium starch glycolate is widely used in oral pharmaceuticals as a disintegrant in capsule and tablet formulations. It is commonly used in tablets prepared by either direct-compression or wet-granulation processes. The usual concentration employed in a formulation is between 2% and 8%, with the optimum concentration of about 4%. Disintegration occurs by rapid uptake of water followed by rapid and enormous swelling. Increasing the tablet compression pressure also appears to have no effect on disintegration time.

HYDROXYPROPYLMETHYL CELLULOSE[65]

1. **Non proprietary names**

BP: Hypromellose JP: Hypromellose PhEur: Hypromellose, USP: Hypromellose

2. **Synonyms**

Benecel MHPC; E464; hydroxyl propyl methylcellulose; HPMC; hydroxylpropylcellulose; Metolose; MHPC; Pharmacoat; Tylopur; Tylose.

3. **Chemical name**

Cellulose hydroxyl propyl methyl ether

4. **Molecular weight**

Molecular weight is approximately 10000-1500000

5. **Functional category**

Bio adhesive material, coating agent, controlled release agent, emulsifying agent, film-forming agent, suspending agent, sustained release agent, tablet binder.

6. **Description**

Hypromellose is an odourless and tasteless, white or creamy-white fibrous or granular powder.

7. **Solubility**

Soluble in cold water, forming a viscous colloid solution; practically insoluble in hot water, chloroform, ethanol (95%) and ether.

8. **Incompatibilities**

Hypromellose is incompatible with some oxidizing agents.

9. **Applications**

Hypromellose is widely used in oral, ophthalmic, nasal and topical pharmaceutical formulations. It is primarily used as a tablet binder, in film coating and as a matrix for use in extended release tablet formulations. Concentrations between 2-5% w/w may be used as a binder in either wet or dry granulation processes. High viscosity grades may be used to retard the release of drugs from a matrix at levels of 10-80% w/w in tablets and capsules. Hypromellose is also used in liquid oral dosage forms as a suspending and thickening agent at concentrations ranging from 0.25-5.0%.

ETHYL CELLULOSE[65]

1. Non proprietary names

BP: Ethyl cellulose, PhEur: Ethyl cellulose, USP-NF: Ethyl cellulose

2. Synonyms

Aqua coat ECD; Aqualon; Ashacel; E462; Ethocel; ethylcellulosam; Sureleas.

3. Chemical name

Cellulose ethyl ether

4. Empirical formula and molecular weight

Ethyl cellulose is partially ethoxylated. Ethyl cellulose with complete ethoxyl substitution (DS = 3) is $C_{12}H_{23}0_6$ ($C_{12}H_{22}0_5$) n $C_{12}H_{23}0_5$ where n can vary to provide a wide variety of molecular weight.

5. Functional category

Coating agent, tablet binder, tablet filler, viscosity increasing agent.

6. Description

Ethyl cellulose is a tasteless, free flowing and white to light tan-colour powder.

7. Solubility

Ethyl cellulose is practically insoluble in glycerine, propylene glycol and water.

8. Incompatibilities

Incompatible with paraffin wax and microcrystalline wax.

9. Applications

Ethyl cellulose is widely used in oral and topical pharmaceutical formulations. The main use of ethyl cellulose in oral formulation is as a hydrophobic coating agent for tablets and granules. Ethyl cellulose coatings are used to modify the release of a drug, to mask an unpleasant taste, or to improve the stability of a formulation. High viscosity grades of ethyl cellulose are used in drug microencapsulation. Ethyl cellulose has also been used as an agent for delivering therapeutic agents from oral (e.g. dental) appliances. In topical formulations, ethyl cellulose is used as a thickening agent in creams, lotions or gels, provided an appropriate solvent is used. Ethyl cellulose is additionally used in cosmetics and food products.

MAGNESIUM STEARATE[65]

1. Non proprietarynames

BP: Magnesium stearate, JP: Magnesium stearate, PhEur: Magnesium stearate USP-NF: Magnesium stearate.

2. Synonyms

Dibasic magnesium stearate; magnesium distearate; magnesia stearates; magnesium octadecanoic acid, magnesium salt; magnesium salt; Stearic acid, magnesium salt; synpro 90.

3. Chemical name

Octadecanoic acid magnesium salt

4. Empirical formula

$C_{36}H_{70}MgO_4$

5. Molecular weight

591.24

6. Functional category

Tablet and capsule lubricant

7. Description

Magnesium stearate is a very fine, light white, impalpable powder of low bulk density, having a faint odour of Stearic acid and a characteristic taste. The powder is greasy to the touch and readily adheres to the skin.

8. Incompatibilities

Incompatible with strong acids, alkalis and iron salts.

9. Applications

Magnesium stearate is widely used in cosmetics, foods and pharmaceutical formulations. It is primarily used as a lubricant in capsule and tablet manufacture at concentrations between 0.25% and 5.0% w/w. Magnesium stearate is hydrophobic and may retard the dissolution of a drug from a solid dosage form; the lowest possible concentration is therefore used in such formulations. It is also used in barrier creams.

MICROCRYSTALLINE CELLULOSE[65]

1. Non-proprietary names

BP: Microcrystalline cellulose, JP: Microcrystalline cellulose, PhEur: cellulose, Microcrystalline, USP-NF: Microcrystalline cellulose.

2. Synonyms

Avicel PH; Cellets; Celex; cellulose gel; hellulosum microcristallinum; Celphere; Ceolus KG; crystalline cellulose; E460; Emcocel; Ethispheres; Fibrocel; MCC Sanaq; Pharmacel; Tabulose; Vivapur.

3. Chemical name

Cellulose

4. Empirical formula

$(C_6H_{10}O_5)$ n where n = 220

5. Functional category

Tablet and capsule diluents, adsorbent; tablet disintegrant, suspending agent.

6. Description

Microcrystalline cellulose is purified, partially depolymerised cellulose that occurs as a white, odourless, tasteless, crystalline powder composed of porous particles. It is commercially available in different particle sizes and moisture grades that have different properties and applications.

7. Solubility

Slightly soluble in 5% w/v sodium hydroxide solution; practically insoluble in water, dilute acids and most organic solvents.

8. Incompatibilities

Microcrystalline cellulose is incompatible with strong oxidizing agents.

9. Applications

Microcrystalline cellulose is widely used in pharmaceuticals, primarily as a binder/diluent in oral tablet and capsule formulations where it is used in both wet granulation and direct compression processes. In addition to its use as binder/diluents, microcrystalline cellulose also has some lubricant and disintegrant properties that make it useful in tableting.

POVIDONE[65]

1. Non-proprietary names

Povidone

2. Synonyms

E1201; Kollidon; Plasdone; poly [1-(2-oxo-1-pyrrolidinyl)ethylene]; polyvidone; polyvinylyrrolidone; povidonum; povipharm; PVP; 1-vinyl-2-pyrrolidinone polymer.

3.Chemical name

1-Ethyneyl-2-pyrrolidinone homopolymer

4. Empirical formula

(C_6H_9NO) n

5. Molecular weight

2500-3,000,000

6. Functional category

Disintegrant, dissolution enhancer, suspending agent, tablet binder.

7. Description

Povidone occurs as a fine, white to creamy-white coloured, odourless or almost odourless, hygroscopic powder. Povidones with K-values equal to or lower than 30 are manufactured by spray-drying and occur as spheres. Povidone K-90 and higher K-value povidones are manufactured by drum drying and occur as plates.

8. Solubility

Freely soluble in acids, chloroform, ethanol (95%), ketones, methanol, and water. Practically insoluble in ether, hydrocarbons and mineral oil.

9. Applications

Povidone is used in variety of pharmaceutical formulations primarily used in solid dosage forms. In tableting, povidone solutions are used as binders in wet granulation processes. It is also added to powder blends in the dry form and granulated *in situ* by the addition of water, alcohol or hydroalcoholic solutions. Povidone is used as a solubilizers in oral and parenteral formulations and has been shown to enhance dissolution of poorly soluble drugs from solid dosage forms. Povidone is also used as a suspending, stabilizing, or viscosity increasing agent in a number of topical and oral suspensions and solutions.

ISOPROPYL ALCOHOL[65]

1. Non proprietary names

BP: Isopropyl Alcohol, JP: Isopropanol, PhEur: Isopropyl Alcohol, USP: Isopropyl Alcohols

2. Synonyms

Alcohol isopopylicus; dimethyl carbinol; IPA; Isopropanol; petrohol; 2-propanol; sec-propyl alcohol; rubbing alcohol.

3. Chemical name

Propan-2-ol

4. Empirical formula

C_3H_8O

5. Molecular weight

60.1

6. Functional category

Disinfectant; solvent

7. Description

Isopropyl alcohol is a clear, colourless, mobile, volatile, flammable liquid with a characteristic, spirituous odour resembling that of a mixture of ethanol and acetone; it has a slightly bitter taste.

8. Solubility

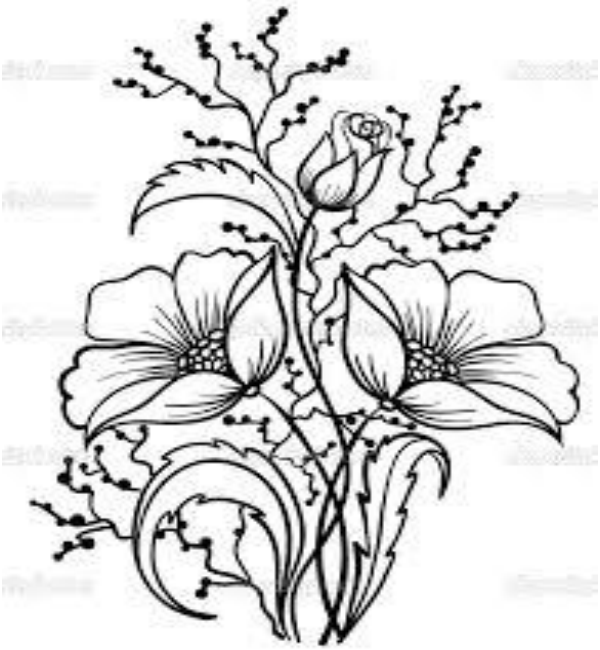
Miscible with benzene, chloroform, ethanol (95%), ether, glycerine, and water.

9. Incompatibilities

Incompatible with oxidizing agents such as hydrogen peroxide and nitric acid, which cause decomposition.

10. Applications

Isopropyl alcohol (propan-2-ol) is used in cosmetics and pharmaceutical formulations. Primarily as a solvent in topical formulations. Although it is used in lotions, the marked degreasing properties of isopropyl alcohol may limit its usefulness in preparations used repeatedly. Isopropyl alcohol is also used as a solvent both for tablet film coating and for tablet granulation, where the isopropyl alcohol is subsequently removed by evaporation.



Materials & Methods

8. MATERIALS AND METHODS

Table 1: List of materials and their applications in formulation

S.NO	NAME OF THE MATERIAL	MANUFACTURE/SUPPLIER	USE IN FORMULATION
1	Lisinopril	Unimark remedies ltd, Chennai.	Active ingredient
2	Glipizide	Unimark remedies ltd, Chennai.	Active ingredient
3	HPMC K100M	Samsung fine chemicals	Hydrophilic polymer
4	Ethyl cellulose	A to Z pharmaceuticals, Chennai.	Hydrophobic polymer
5	Sodium starch glycolate	S.D. fine chemicals, Mumbai.	Super disintegrant
6	Polyvinyl pyrrolidone K 30	S.D. fine chemicals, Mumbai.	Binder
7	Magnesium stearate	S.D. fine chemicals, Mumbai.	Lubricant
8	Talc	S.D. fine chemicals, Mumbai.	Glidant
9	Microcrystalline cellulose	Vikaas chemicals, Chennai.	Diluent
10	Isopropyl alcohol	Supra chemicals, Chennai.	Solvent
11	Lake poncea 4R	Zudila Enterprises, China.	Colouring agent

Table 2: List of instruments/equipments

S.NO	Equipments / Instruments	Manufacture/Supplier
1	Electronic weighing balance	Shimadzu, Japan.
2	Hot air oven	Industrial heaters, Chennai.
3	10 station compression machine	Rimek, India.
4	Digital vernier calliper	Mitutoyo, Japan.
5	Monsanto hardness tester	Erweka, Mumbai.
6	Friabilator	Roche, India.
7	pH meter	Symchrony, India.
8	Sonicator	.Leela electronics, Chennai.
9	Disintegrstion apparatus	Veego, Mumbai.
10	Dissolution apparatus	Veego, Mumbai
11	UV – Visible Spectrophotometer	Shimadzu, Japan.
12	Fourier Transform Infra Red Spectrophotometer	Nicolet, India.
13	Stability chamber	Technico, India.
14	Moisture analysis	Sartorius, German.

METHODOLOGY

1. PREFORMULATION STUDIES[66]

Pre-formulation study is the process of optimizing the delivery of drug through determination of physicochemical properties of the new compound that could affect drug performance and development of an efficacious, stable and safe dosage form. It is the first step in rational development of drug dosage forms of a drug substance. It provides the information required to define the nature of the drug and a frame work for the drug combination with pharmaceutical excipients in dosage form.

A. Organoleptic properties

The colour, odour and taste of the drugs were studied.

B. Particle size and shape

Particle size and shape of the drugs were studied by optical microscopic method.

C. Melting point

Melting points of the drugs were confirmed by capillary tube method.

D. Solubility analysis

Solubility is the important parameter for preformulation studies because,

1. It affects the dissolution of the drug.
2. Bioaviability of drug is directly affected by oral administration and also by dissolution.
3. Particle size, shape, surface area may affect the dissolution characteristics of drug hence it should be determined during preformulation.

Method : Weighed quanditity of drug was added to the suitable volume of solvent and solubility checked.

E. Loss on drying (%)

1g of drug was accurately weighed and dried in an oven at 105° C for 3 hours. By gentle sidewise shaking, the sample was distributed at the specified temperature for constant weight. The drug sample was allowed to come to room temperature in a desiccators before weighing.

The difference between successive weights should not be more than 0.5mg

The loss on drying is calculated by the formula:

$$\% \text{ LOD} = \frac{W3 - W2}{W2 - W1} X100$$

Where,

W1 – Weight of empty weighing bottle

W2 – Weight of weighing bottle + sample

W3 – Weight of weighing bottle + dried sample

DRUG EXCIPIENT COMPATIBILTY STUDY

The drug and the excipients chosen for the formulations were screened for compatibility by physical methods and Fourier Transform Infrared spectroscopic studies.

Physical compatibility study[66]

The physical compatibility studies were conducted to provide valuable information to the formulator in selecting the appropriate excipients for the formulation. It was done by mixing the drugs and the excipients and kept at room temperature and at 40° C and 75% RH. Any change in colour of the physical mixture was observed visually.

Chemical compatibility study by FTIR[67]

Infrared spectroscopy can be used to identify a compound and also to investigate the composition of the mixture. Pure drugs, polymers, excipients, drug excipient mixture was subjected to FTIR studies to investigate the drug- excipient interactions. The IR spectra of the test samples were obtained by pressed pellet technique using potassium bromide.

PREPARATION OF BUFFER SOLUTIONS[4]

Preparation of 0.1M (pH 1.2) Hydrochloric acid

8.5ml of the hydrochloric acid was taken, dissolved in water and made upto 1000ml to get 0.1M hydrochloric acid.

Preparation of pH 6.8 phosphate buffer solution

Take 50ml of 0.2M potassium dihydrogen phosphate in a 200ml volumetric flask and add 22.4ml of 0.2 M sodium hydroxide solution, then the volume was made upto 200ml using distilled water.

Preparation of 0.2M potassium dihydrogen phosphate

27.218 g of potassium dihydrogen phosphate was dissolved in distilled water and the volume was made upto 1000ml using distilled water.

Preparation of 0.2 M Sodium hydroxide

8g of sodium hydroxide was dissolved in distilled water and made upto 1000ml with distilled water.

CALIBRATION CURVE

For Lisinopril[34]

100mg of drug was weighed and transferred to a 100ml standard flask and made upto volume using 0.1M HCl. 10ml of the stock solution was pipetted out into separate 100ml standard flask and made upto the volume using 0.1M HCl. From the resulting solution 2, 4, 6, 8 and 10 ml were pipette out into five separate 100ml standard flasks and made upto volume using 0.1M HCl to represent 2, 4, 6, 8 and 10 µg/ml of the drug. The absorbance of the solutions was measured at 207nm taking 0.1M HCl as blank using UV – Visible spectrophotometer. The calibration curve was then plotted taking concentration (µg/ml) along X-axis and absorbance along Y- axis.

For Glipizide[47]

100mg of drug was weighed and transferred to a 100ml standard flask and made upto volume using pH 6.8 phosphate buffer. 10ml of the stock solution was pipetted out into separate 100ml standard flask and made upto the volume using pH 6.8 phosphate buffer. From the resulting solution 2, 4, 6, 8 and 10 ml were pipette out into five separate 100ml standard flasks and made upto volume using pH 6.8 phosphate buffer to represent 2, 4, 6, 8 and 10 µg/ml of the drug. The absorbance of the solutions was measured at 207nm taking pH 6.8 phosphate buffer as blank using UV – Visible spectrophotometer. The calibration curve was then plotted taking concentration (µg/ml) along X-axis and absorbance along Y- axis.

PRECOMPRESSION STUDIES OF DRUG AND BLEND

FLOW PROPETY MEASUREMENTS[66]

The flow properties of powders are critical for an efficient tabletting operation. A good flow of the powder or granulation to be compressed is necessary to assure efficient mixing and acceptable weight uniformity for the compressed tablets. The flow property measurements include bulk density, tapped density, compressibility index, Hausner's ratio and angle of repose. The flow property measurements of drug and blend were determined to select the type of granulation technique to be carried out for the formulation.

A. BULK DENSITY[71]

It is the ratio of total mass of powder to the bulk volume of powder. It was measured by pouring the weighed powder into a measuring cylinder and initial weight was noted. This initial volume was called the bulk volume. From this the bulk density was calculated according to the formula mentioned below. It is expessed in g/ml and is given by

$$\rho_b = M / V_b$$

where, M and V_b are mass of powder and bulk volume of the powder respectively.

B. TAPPED DENSITY (ρ_t)[71]

It is the ratio of weight of the powder to the tapped volume of powder. The powder was introduced into a measuring cylinder with the aid of funnel and tapped for 500 times on a wooden surface at a 2 sec interval and the volume attained is the tapped volume. It is expressed in g/ml and is given by

$$\rho_t = M / V_t$$

where, M and V_t are mass of powder and tapped volume of the powder respectively.

C. ANGLE OF REPOSE[71]

The flow properties were characterized in terms of angle of repose, carr's index and Hausner's ratio. For determination of angle of repose (θ), the drug and the blend were poured through the walls of a funnel, which was fixed at a position such that its lower tip was at a height of exactly 2.0cm above hard surface.

The drug or the blends were poured till the time when upper tip of the pile surface touched the lower tip of the funnel. Angle of repose was calculated using following equation.

$$\Theta = \tan^{-1} (h/r)$$

Where, h= height of the pile in cm; r = radius of the pile in cm.

D. CARR'S INDEX OR % COMPRESSIBILITY[71]

It indicates powder flow properties. It is measured for determining the relative importance of interparticulate interactions. It is expressed in percentage and is given by,

$$CI = \frac{\rho_t - \rho_b}{\rho_t} X\ 100$$

where, ρ_t and ρ_b are tapped density and bulk density respectively.

E. HAUSNER'S RATIO[71]

Hausner's ratio is an indirect index of ease of powder flow. It is calculated by the following formula.

$$HR = \rho_t / \rho_b$$

Where, ρ_t and ρ_b are tapped density and bulk density respectively.

TABLE 3: VALUES OF ANGLE OF REPOSE, COMPRESSIBILITY INDEX AND HAUSNER'S RATIO[69]

Flow property	Angle of Repose (θ)	Compressibilty Index	Hausner's Ratio
Excellent	25-30	<10	1.00-1.11
Good	31-35	11-15	1.12-1.18
Fair	36-40	16-20	1.19-1.25
Passable	41-45	21-25	1.26-1.34
Poor	46-55	26-31	1.35-1.45
Very poor	56-65	32-37	1.46-1.59
Very very poor	>65	>38	>1.60

Formulation Development

9. FORMULATION DEVELOPMENT

Formulation of Immediate release granules of Lisinopril[9]

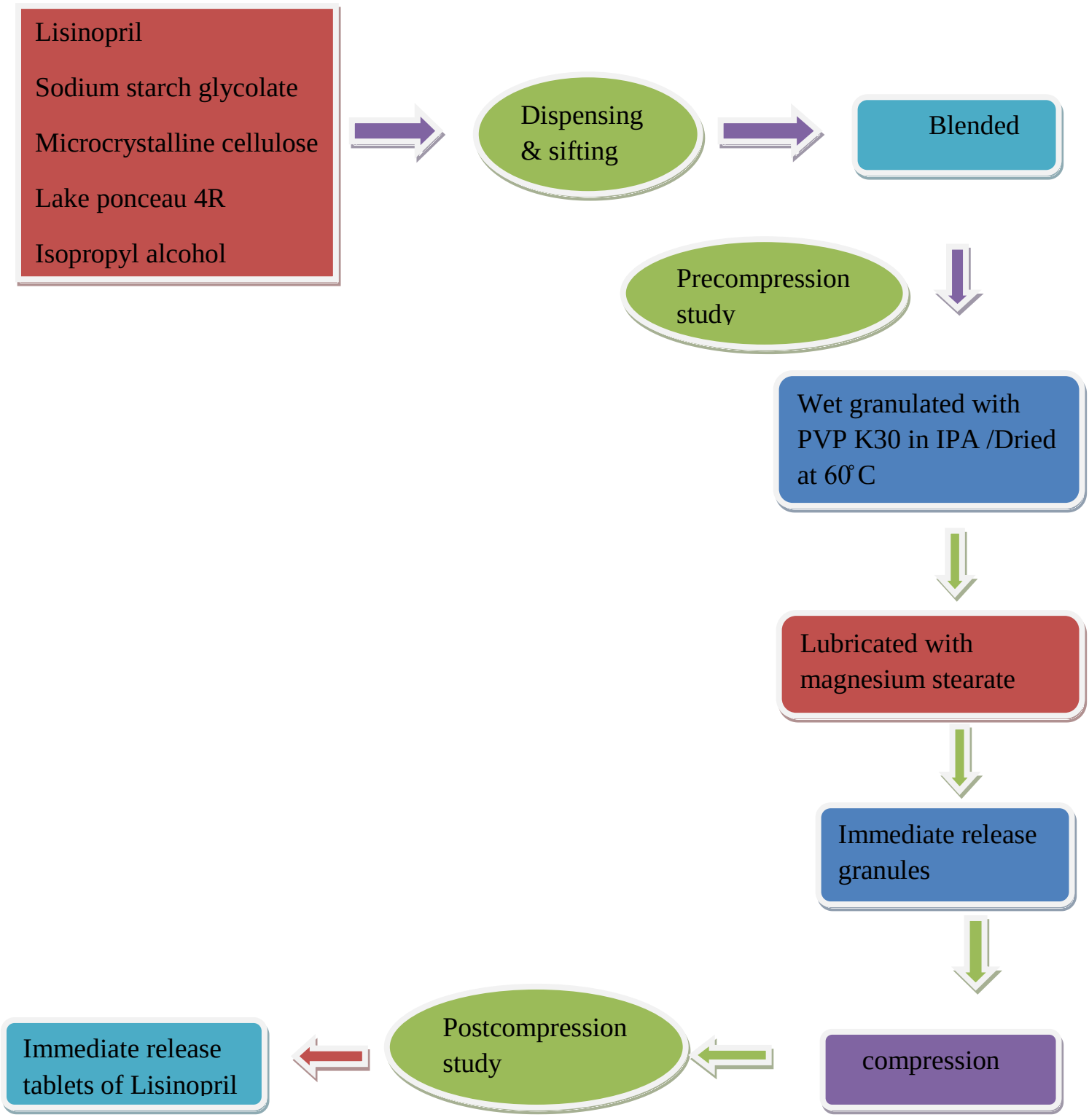
Lisinopril belongs to class III drug in BCS classification i.e. high solubility and low permeability. But it has half life period 12 hours. To improve the onset of action the immediate granules of Lisinopril were prepared by wet granulation technique. Sodium starch glycolate (SSG) was used as a super disintegrant in 4%, 6% and 8% concentrations to improve the dissolution of the drug. The granules were compressed by 10 station compression machine.

Table 4: Composition of immediate release granules

S.NO	Ingredients	L-1(mg)	L-2(mg)	L-3(mg)
1	Lisinopril	10	10	10
2	Sodium starch glycolate	8	12	16
3	Polyvinyl pyrrolidone K-30	8	8	8
4	Magnesium stearate	4	4	4
5	Talc	2	2	2
6	Microcrystalline cellulose	175	173	169
7	Lake ponceau 4R	1	1	1
8	Isopropyl alcohol	q.s	q.s	q.s
Total weight		200	200	200

The immediate release tablet of Lisinopril was formulated and optimized. The optimized formulation was used for the final bilayer tablets.

Flow chart for formulation of Lisinopril immediate release (IR) tablets



FORMULATION OF GLIPIZIDE SUSTAINED RELEASE TABLETS

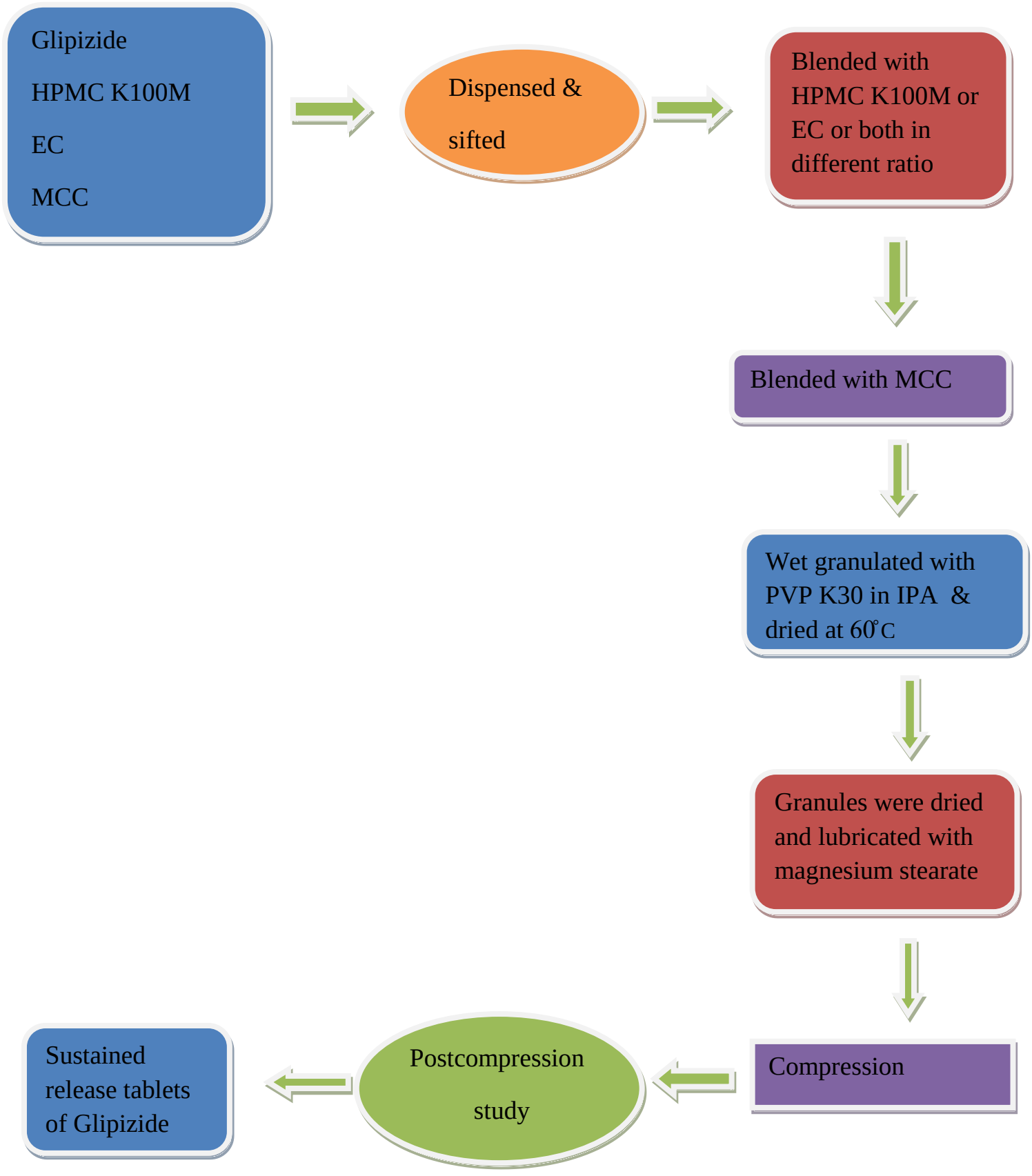
The sustained release granules were prepared by wet granulation technique. Different polymers such as HPMC K 100 M and Ethyl cellulose were used in different ratios. The tablets were compressed by 10 station compression machine using mm punches. The optimized batch of sustained release tablets of Glipizide was then compressed with the optimized batch of immediate release Lisinopril tablets to get bilayer tablets.

Table 5: Composition of sustained release granules

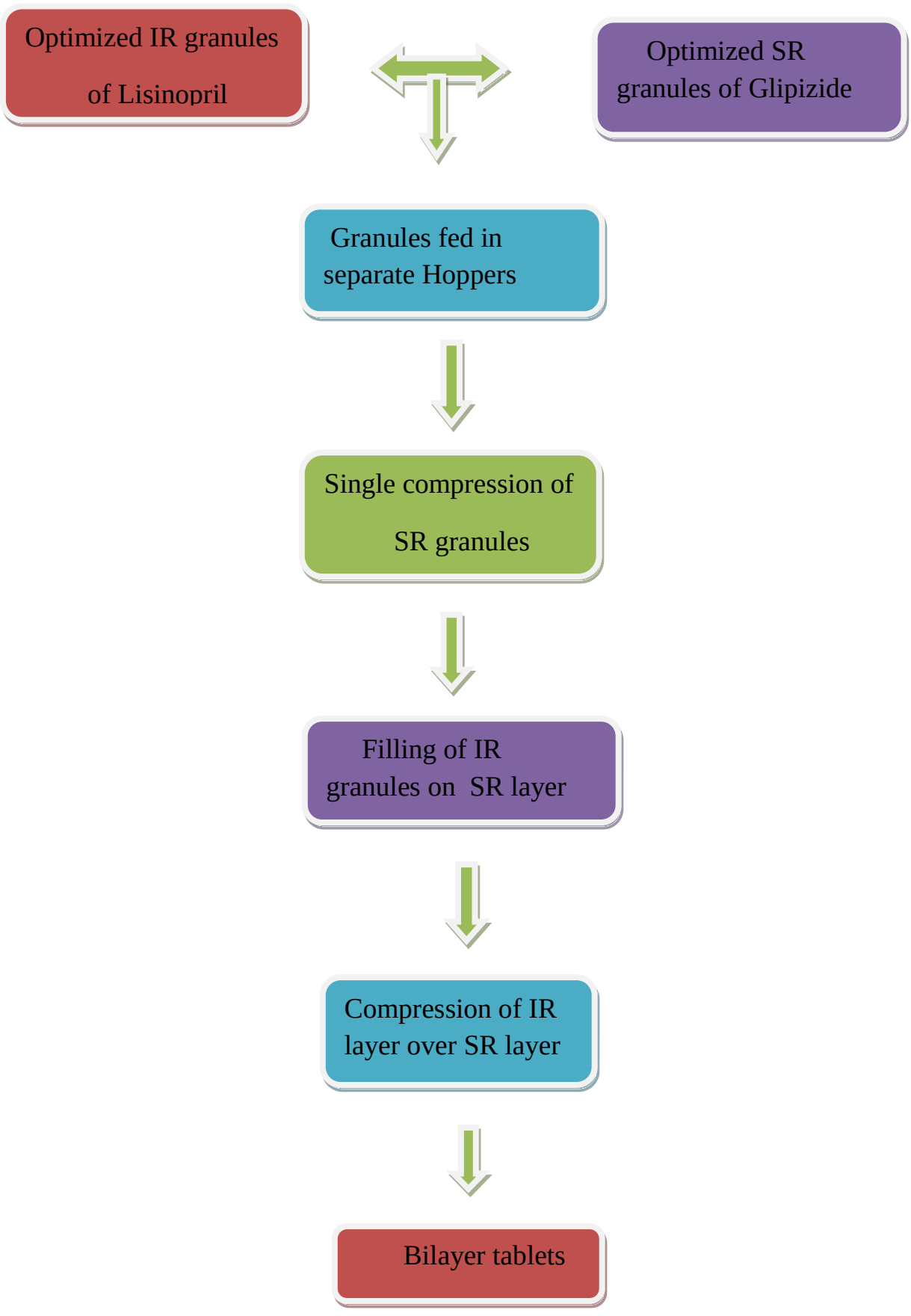
S.NO	Ingredients	G-1(mg)	G-2(mg)	G-3(mg)	G-4(mg)	G-5(mg)
1	Glipizide	10	10	10	10	10
2	HPMC K100 M	-	50	25	50	75
3	Ethyl cellulose	50	-	25	25	25
4	Polyvinyl pyrrolidone	12.5	12.5	12.5	12.5	12.5
5	Magnesium stearate	10	10	10	10	10
6	Talc	2.5	2.5	2.5	2.5	2.5
7	Microcrystalline cellulose	165	165	165	140	115
8	Isopropyl alcohol	q.s	q.s	q.s	q.s	q.s
Total weight		250	250	250	250	250

The sustained release tablet of Glipizide was formulated and optimized. The optimized formulation was used for the final bilayer tablets.

Flow chart for sustained release tablets (SR) of Glipizide



Flow chart for bilayer tablets of Lisinopril(IR) and Glipizide(SR)



1. POST COMPRESSION STUDIES

A. PHYSICAL PARAMETERS

1. General appearance

The general appearance of the tablets from each formulation batch was observed. The general appearance parameters such as shape, colour, presence or absence of odour and taste were evaluated visually.

2. Uniformity of weight[4]

Twenty tablets were randomly selected from each batch and individually weighed. The average weight and standard deviation of 20 tablets was calculated. The batch passes the test for weight variation, if not more than two of the individual weight deviates from the average weight by more than the percentage shown in the Table and none should deviate by more than twice the percentage shown. The average weight and standard deviation of the tablets of each batch were given in the table.

Table 6: IP limit for uniformity of weight

Average weight of tablet	Percentage deviation
80 or less	10
80 to 250	7.5
More than 250	5

3. Thickness and diameter[4]

The control of physical dimension of the tablet such as thickness and diameter are essential for consumer acceptance and to maintain uniformity of tablet weight. Six tablets were selected from each batch and their thickness and diameter were measured by using vernier callipers. The average thickness and diameter with standard deviation of the tablets from each batch were calculated and tabulated.

4. Hardness[4]

The tablet crushing load is the force required to break a tablet by compression. Hardness was measured by using hardness tester. For each batch, six tablets were selected randomly and evaluated. Hardness of about4-6 kg/cm ^{2} is considered to be minimum for uncoated tablets and for mechanical stability.

5. Friability[4]

Friability test is performed to assess the effect of friction and shocks, which may often cause tablet to chip, cap or break. Roche friabilator was used for this purpose. Preweighed sample of twenty tablets were placed in the friabilator, which was then operated for 100 revolutions. After 100 revolutions the tablets were dusted and reweighed. Compressed tablets should not lose more than 1% of their weight.

% Friability= Initial Weight–Final Weight/ Final Weight X 100

6. Disintegration[4]

Randomly six tablets were selected from each batch for disintegration test. Disintegration test was performed without disc in simulated gastric fluid (37 ± 0.5 °C) using United States Pharmacopeia (USP) disintegration apparatus. The mean standard deviations (SD) of six tablets were calculated.

B. DRUG CONTENT

1. FOR IR TABLETS CONTAINING LISINOPRIL[34]

Twenty tablets were selected randomly, weighed and finely grounded. An accurately weighed quantity of powder equivalent to 10mg of Lisinopril was transferred to a 100ml volumetric flask and dissolved. The volume was made upto the mark with 0.1M HCl. From this solution 10ml was taken and further diluted with 0.1M HCl in a 100ml volumetric flask. The absorbance of the resulting solution was measured at 207nm taking 0.1M HCl as blank using UV-Visible spectrophotometer. The concentration was obtained from the calibration graph.

2. FOR SR TABLETS CONTAINING GLIPIZIDE[47]

Twenty tablets were selected randomly, weighed and finely grounded. An accurately weighed quantity of powder equivalent to 50mg of Glipizide was transferred to a 100ml volumetric flask and dissolved in 5ml of 0.1N NaOH and the volume was made upto the mark with pH 6.8 phosphate buffer. From this solution 10ml was taken and further diluted with pH 6.8 phosphate buffer in a 100ml volumetric flask. From this solution 5ml was taken and diluted with pH 6.8 phosphate buffer in 50ml volumetric flask. The absorbance of the resulting solution was measured at 276nm taking pH 6.8 phosphate buffer as blank using UV-Visible spectrophotometer. The concentration was obtained from the calibration graph.

C. BILAYER TABLETS OF LISINOPRIL AND GLIPIZIDE (SIMULTANEOUS EQUATION METHOD)[72]

Simultaneous estimation of Lisinopril and Glipizide was carried out using UV-Visible spectrophotometer.

PROCEDURE[70]

The following equations were used to determine the contents.

$$Cx = \frac{A_2 a_{y1} - A_1 a_{y2}}{a_{x2}\, a_{y1} - a_{x1} a_{y2}}$$

$$Cy = \frac{A_1 a_{x1} - A_2 a_{x1}}{a_{x2}\, a_{y1} - a_{x1} a_{y2}}$$

where, $a_{x1}$and a_{x2} = The absorptivity of drug X at λ_1 and λ_2 respectively.

$a_{y1}$and a_{y2} = The absorptivity of drug Y at λ_1 and λ_2 respectively.

$A_1$and A_2= The absorbance of sample at λ_1 and λ_2 respectively.

$$(A_1/A_2) /(a_{x1}/a_{x2}) \text{ and } (a_{y1}/a_{y2}) / (A_1/A_2)$$

The ratios should lie outside the range of 0.1 – 2.0 for the precise determination of X and Y drugs. This criteria is satisfied only when the λ_{max} of the two components is reasonably dissimilar and the components should not interact chemically.

1. Preparation of standard stock solution of Lisinopril[9]

Lisinopril equivalent to 100mg was accurately weighed and dissolved. The volume was made upto mark with pH 6.8phospahte buffer in 100ml standard flask. From this solution 10ml was taken and diluted with pH 6.8phospahte buffer in 100ml volumetric flask. From this solution 10ml was taken and further diluted with pH 6.8phospahte buffer in 100ml standard flak.

2. Preparation of standard stock solution of Glipizide[47]

Glipizide equivalent to 100mg was accurately weighed and dissolved. The volume was made upto mark with pH 6.8phospahte buffer in 100ml standard flask. From this solution 10ml was taken and diluted with pH 6.8phospahte buffer in 100ml volumetric flask. From this solution 10ml was taken and further diluted with pH 6.8phospahte buffer in 100ml standard flak.

3. Preparation of sample solution

Twenty tablets were selected randomly, weighed and finely grounded. An accurately weighed quantity of powder equivalent to 100mg of Glipizide was transferred to a 100ml volumetric flask and dissolved in 5ml of 0.1N NaOH and the volume was made upto the mark with pH 6.8 phosphate buffer. From this solution 10ml was taken and further diluted with pH 6.8 phosphate buffer in a 100ml volumetric flask. From this solution 10ml was taken and further diluted with pH 6.8 phosphate buffer in a 100ml volumetric flask. The absorbance of resulting solution was measured at 207nm and 276nm respectively. The amounts of both the drugs were determined.

D. *IN VITRO* DISINTEGRATION STUDIES FOR IR TABLETS

The disintegration time was determined using disintegration test apparatus. The tablets were placed in each of the six tubes of the basket. The assembly was suspended in 0.1M HCl maintained at a temperature of 37° C ± 2° C and the apparatus was switched on. The time taken to disintegrate the tablets completely was noted.

E. *IN VITRO* DISSOLUTION STUDIES[42]

1. For IR tablets

The release of Lisinopril was determined using Type II (paddle) dissolution apparatus under sink condition. 900ml of 0.1M HCl was used as dissolution medium at a temperature of 37° C ± 0.5° C. The paddle was stirred at a speed of 50 rpm. The release studies were carried out for 30mins. The absorbance of the solution was measured at 207nm taking 0.1M HCl as blank using UV-Visible spectrophotometer.

2. For SR tablets

The release of Glipizide was determined using Type II (paddle) dissolution apparatus under sink condition. 900ml of pH 6.8 phosphate buffer was used as dissolution medium at a temperature of 37° C ± 0.5° C. The paddle was stirred at a speed of 50 rpm. The release studies were carried out for 24hours. The absorbance of the solution was measured at 276nm taking pH 6.8 phosphate buffer as blank using UV-Visible spectrophotometer.

3. For bilayer tablets

The release of bilayer tablet was determined using Type II (paddle) dissolution apparatus under sink condition. 900ml of 0.1M HCl was used as dissolution medium for first two hours followed by pH 6.8 phosphate buffer solution for next eight hours maintained at a temperature of 37° C ± 0.5° C. The paddle was stirred at a speed of 50 rpm. The release studies were carried out for ten hours. The absorbance of the solution was measured at 207nm and 276nm taking respective buffer solutions as blank using UV-Visible spectrophotometer and the calculations were done by simultaneous equation method.

F. EVALUATION OF *IN VITRO* RELEASE KINETICS[73, 74]

To study the in vitro release kinetics of the optimized bilayer tablets, data obtained from *in vitro* dissolution study were plotted in various kinetic models.

1. Zero order equation

Zero order equation assumes that the cumulative amount of drug release is directly related to time. The equation maybe as follows:

$$C=k_0t$$

Where, K_0 is the zero order rate constant expressed in unit concentration/time and the time in hour. A graph of concentration vs time would yield a straight line with a slope equal toK_0 and intercept the origin of the axis.

2. First order equation

The release behaviour of first order equation is expressed as log cumulative percentage of drug remaining vs time. The equation may be as follows.

$$\text{Log } C = \text{Log } C_0 - kt/2.303$$

Where C = The amount of drug un-dissolved at t time, C_0= Drug concentration at t = 0, k= Corresponding release rate constant.

3. Higuchi kinetics

The Higuchi release model describes the cumulative percentage of drug release vs square root of time. The equation may be as follows

$$Q = K\sqrt{t}$$

Where, Q = the amount of drug dissolved at time t. K is the constant reflecting the design variables of the system. Hence, drug release rate is proportional to the reciprocal of the square root of time.

4. Hixson and crowell erosion equation

To evaluate the drug release with changes in the surface area and the diameter of particles, the data were plotted using the Hixson and Crowell erosion equation. The graph was plotted by cube root of % drug remaining Vs Time in hours.

$$Q_0^{1/3} - Q_t^{1/3} = K_{HC} \text{ X } t$$

Where, Q_t – amount of drug released at time t, Q_0 – initial amount of drug, K_{HC}– rate constant for Hixson Crowell equation.

5. Korsmeyer – Peppas equation

Korsmeyer *et al* developed a simple, semi-empirical model relating exponentially the drug release to the elapsed time. The equation may be as follows:

$$Q/Q_0 = Kt^n$$

Where, Q/Q0= The fraction of drug released at time t, k = Constant comprising the structural geometric characteristics, n = The diffusion exponent that depends on the release mechanism.

Table 7: Diffusion exponent and solute release mechanism for cylindrical shape

Diffusion exponent (n)	Overall solute diffusion mechanism
0.45	Fickian diffusion
0.45 < n < 0.89	Anomalous (non-fickian) diffusion
0.89	Case II transport
n > 0.89	Super case II transport

G. STABILITY STUDY

Stability studies of optimized bilayer tablets were carried out according to ICH guidelines. All the tablets were packed in blisters and kept in a humidity chamber at 40 ± 2° C and 75 ± 5% RH for 3 months. Samples were withdrawn at monthly intervals and analyzed for physical characteristics, hardness and *in vitro* dissolution.

Results & Discussion

10. RESULTS AND DISCUSSION

The present work was aimed to formulate bilayer tablets of immediate release Lisinopril and sustained release Glipizide. The therapy with these drugs offers a good quality of life for patients who are suffering from hypertension and type II diabetes mellitus.

PREFORMULATION STUDIES

DRUG CHARACTERIZATION

LISINOPRIL

Lisinopril raw material obtained from Unimark remedies limited was tested as per in house specification and the results are listed. The drug source is identified and found complying with the specifications.

Table 8: Identification of Lisinopril

S.NO	TEST	SPECIFICATION	RESULTS
1	Description	A white crystalline powder	A white crystalline powder
2	Loss on drying	Maximum 0.4% W/W	0.23% W/W
3	Solubility	Soluble in water, very slightly soluble in ethanol (95%)	complies
4	Melting point	146° C - 148° C	145° C - 149° C

GLIPIZIDE

Glipizide raw material obtained from Unimark remedies limited was tested as per in house specifications and the results are listed. The drug source is identified and found complying with the specifications.

Table 9: Identification of Glipizide

S.NO	TEST	SPECIFICATION	RESULTS
1	Description	A white or almost white, crystalline powder	A white crystalline powder
2	Loss on drying	Not more than 0.5% W/W	0.26% W/W
3	Solubility	Practically insoluble in water, very slightly soluble in methylene chloride & in acetone. Practically insoluble in ethanol(96%) It dissolves in dilute solutions of alkali hydroxides.	Complies
4	Melting point	208° C- 209° C	207° C -208° C

DRUG EXCIPIENT COMPATIBILITY STUDY

Physical compatibility study

The compatibility studies were carried out to study the possible interactions between active ingredients (Lisinopril & Glipizide) and inactive ingredients. Physical mixtures of both API and excipients were prepared separately as per the ratios mentioned in table below and kept for stability at 40° C and 75% RH for one month. Samples were taken out after every 10days and were subjected to physical and chemical compatibility tests. The physical compatibility of drug and excipients are given.

Table 10: Physical compatibility study drugs and excipients

S.NO	Drug + excipient	Description and condition				comments
		Initial	Room temperature and 40° C / 75% RH in days			
			10th	20th	30th	
1	Lisinopril	A white crystalline powder	NC	NC	NC	Compatible
2	Glipizide	White or almost white crystalline powder	NC	NC	NC	Compatible
3	Lisinopril +Glipizide	White crystalline powder	NC	NC	NC	Compatible
4	Sodium starch glycolate	White or almost white powder	NC	NC	NC	Compatible
5	Magnesium stearate	Light white powder	NC	NC	NC	Compatible
6	Polyvinyl pyrrolidone	White to creamy white powder	NC	NC	NC	Compatible
7	Talc	White to greyish white powder	NC	NC	NC	Compatible
8	HPMC K 100M	White or creamy white powder	NC	NC	NC	Compatible
9	Ethylcellulose	A white colour powde	NC	NC	NC	Compatible
10	Microcrystalline cellulose	A white crystalline powder	NC	NC	NC	Compatible
11	Lisinopril +SSG	White or almost white powder	NC	NC	NC	Compatible
12	Lisinopril +magnesium steara	White powder	NC	NC	NC	Compatible
13	Lisinopril +MCC	A white crystalline powder	NC	NC	NC	Compatible

14	Lisinopril +PVP K30	Creamy white powder	NC	NC	NC	Compatible
15	Glipizide + HPMC K100M	White to creamy white powder	NC	NC	NC	Compatible
16	Glipizide+ EC	Free flowing white coloured powder	NC	NC	NC	Compatible
17	Glipizide+ PVP K30	White to creamy white Hygroscopic powder	NC	NC	NC	Compatible
18	Glipizide+ Magnesium stearate	White crystalline Powder	NC	NC	NC	Compatible
19	Glipizide + MCC	White or white crystalline powder	NC	NC	NC	Compatible
20	Lake ponceau 4R	Red coloured soft powder	NC	NC	NC	Compatible
21	Lisinopril+ Lake ponceau 4R	White to light red cloued powder	NC	NC	NC	Compatible
22	Lisinopril+ Talc	White to ceamy white powder	NC	NC	NC	Compatible
23	Glipizide+ Talc	White to ceamy white powder	NC	NC	NC	Compatible

NC – No change

The physical compatibility study was performed visually. The study implies that the drug and the excipients were physically compatible with each other as there was no change of physical parameters. The excipients which are compatible with the drug were selected for the formulation.

Chemical compatibility study

All the samples were scanned at the wave number region of 4000-400 cm^{-1}using KBr disc method. This KBr discs were formed by taking drug and KBr in a ratio of 1: 100 respectively. Then this mixture was mixed well in mortar for three to five minutes. A very small amount of this mixture was uniformly spread and sandwiched between the pellets and pressed using KBr pellet press at a pressure of 20,000 psi for 1min.The pressure was then released and pellet was placed into the pellet holder and thus scanned in the IR region.

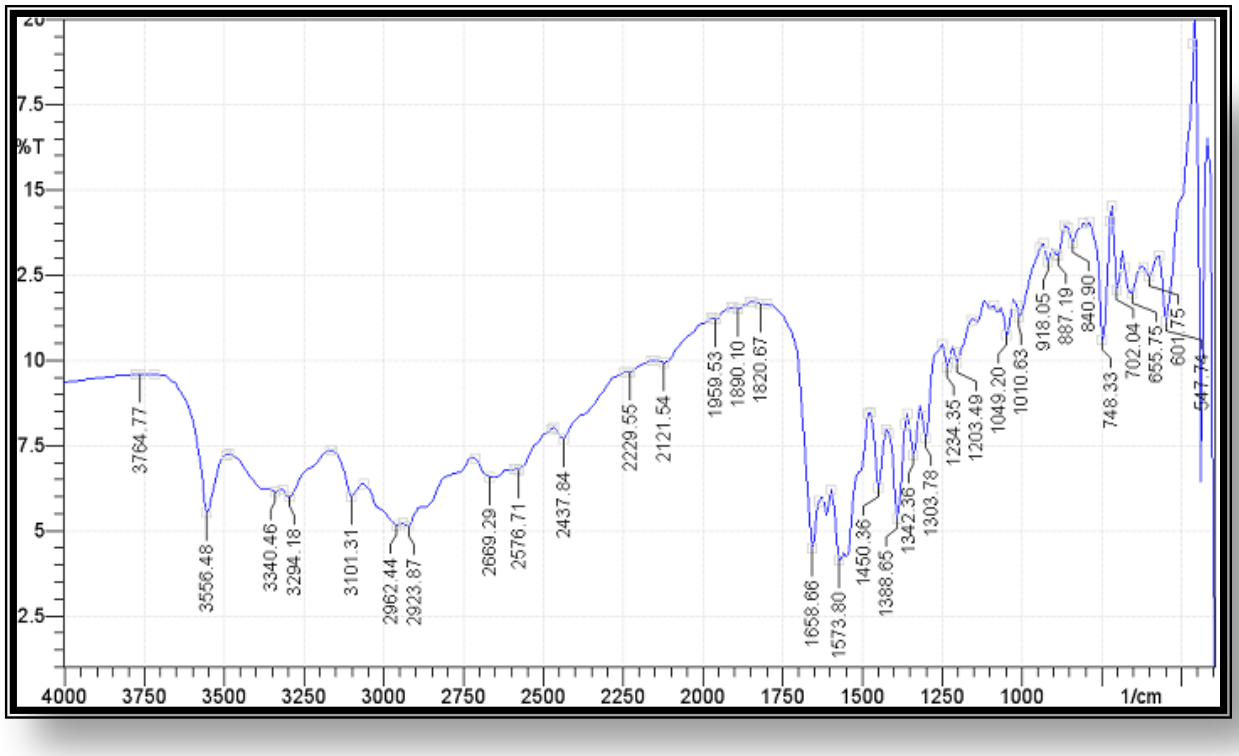


Fig 14: FTIR of Lisinopril

Table 11:IR Spectral Interpretation of Lisinopril

S.NO	Functional group	Observed peak
1	O-H (Carboxylic acid) stretching	3340 cm^{-1}
2	N-H (Primary amine) stretching	3340 cm^{-1}
3	C=O (Carboxylic acid) stretching	1658 cm^{-1}
4	N-H (secondary amine) stretching	3294 cm^{-1}
5	C-H (alkane) stretching	2923 cm^{-1}
6	C-H (Aromatic) stretching	3101cm^{-1}
7	C=N	1658 cm^{-1}

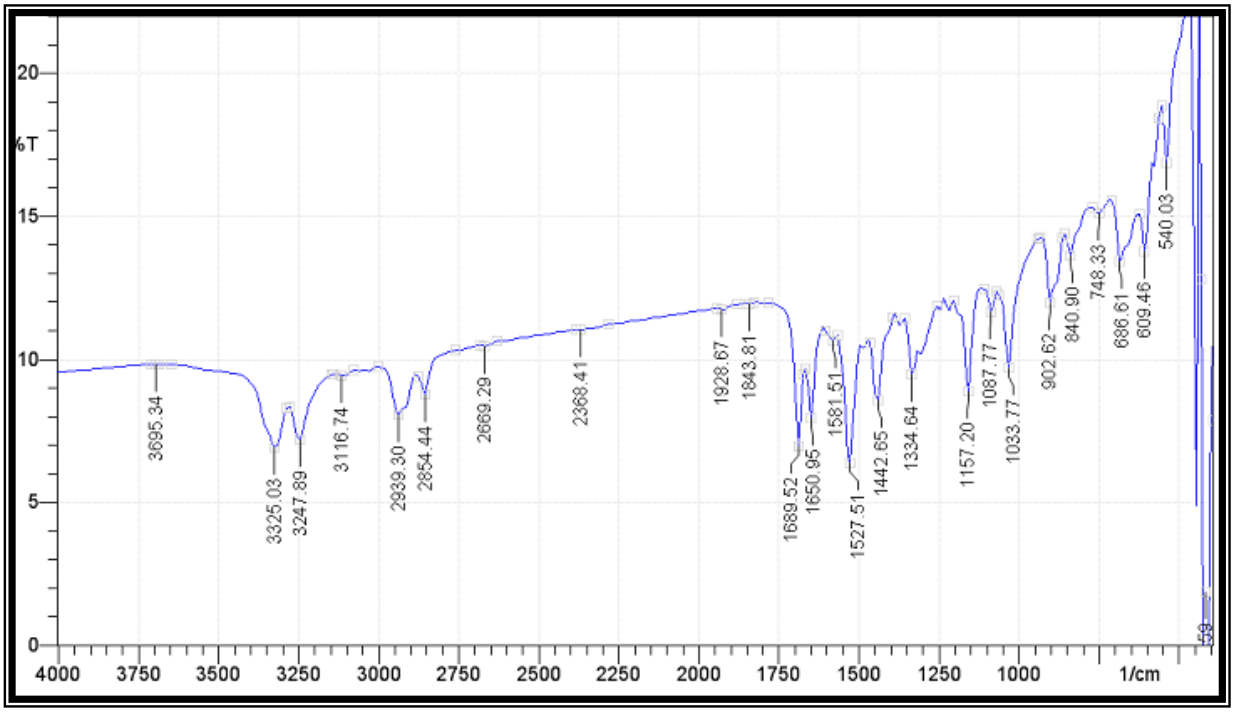


Fig 15: FTIR of Glipizide

Table 12: IR Spectral Interpretation of Glipizide

S.NO	Functional group	Observed peak
1	N-H (Primary amine) stretching	3247 cm^{-1}
2	C=O (Carboxylic acid) stretching	1689 cm^{-1}
3	C-H (alkane) stretching	2854 cm^{-1}
4	C-H (Aromatic) stretching	3116 cm^{-1}

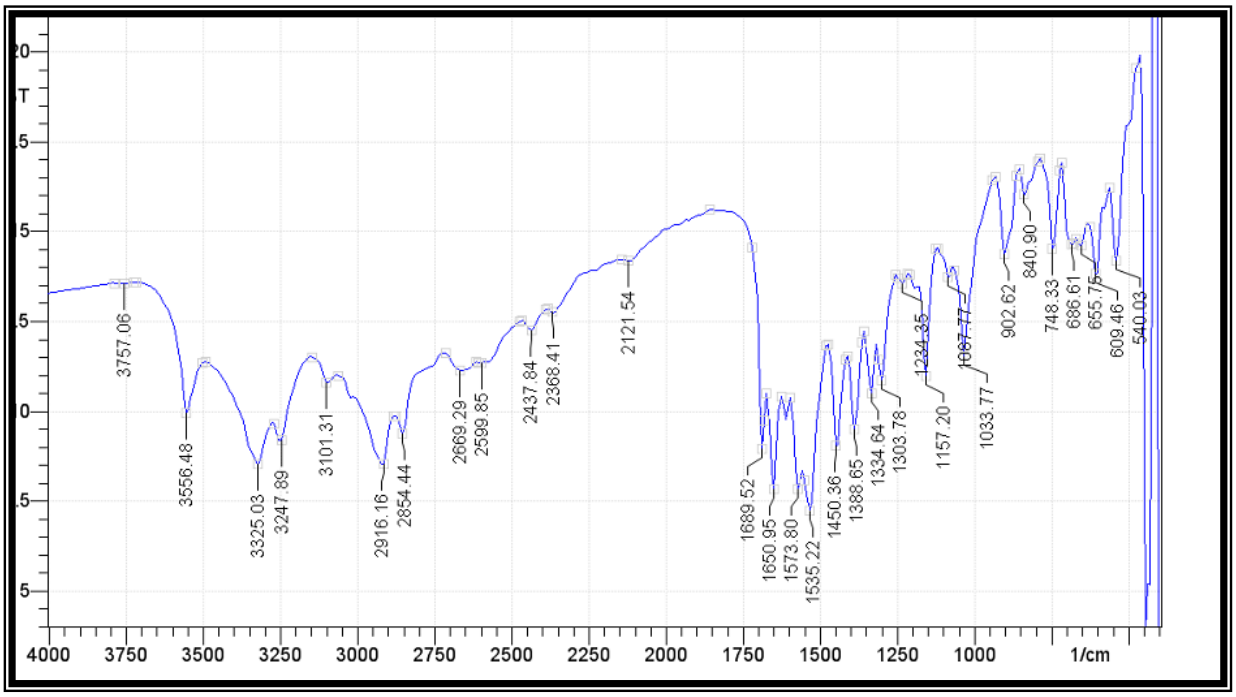


Fig 16: FTIR of Lisinopril and Glipizide

Table 13: IR Spectral Interpretation of Lisinopril and Glipizide

S.NO	Functional group	Observed peak
1	O-H (Carboxylic acid) stretching	3325 cm^{-1}
2	C=O (Carboxylic acid) stretching	1689 cm^{-1}
3	N-H (secondary amine) stretching	3247 cm^{-1}
4	C-H (alkane) stretching	2854 cm^{-1}
5	C-H (Aromatic) stretching	3101cm^{-1}
6	C=N	1650 cm^{-1}

INFERENCE

No shift and no disappearance of characteristic peaks suggesting that there is no interaction between the drugs and also with the excipients in the final formulation.

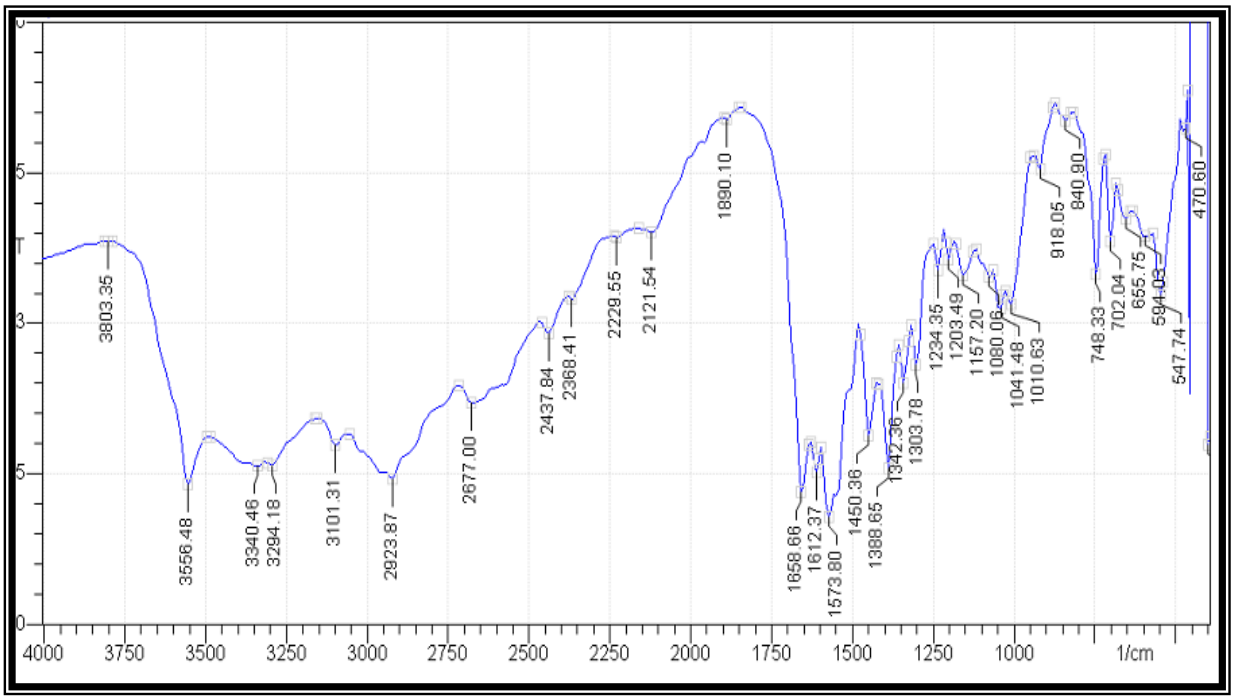


Fig 17: FTIR of Lisinopril and sodium starch glycolate

Table14: IR Spectral Interpretation of Lisinopril and sodium starch glycolate

S.NO	Functional group	Observed peak
1	O-H (Carboxylic acid) stretching	3340 cm^{-1}
2	N-H (secondary amine) stretching	3294 cm^{-1}
3	C-H (alkane) stretching	2923 cm^{-1}
4	C-H (Aromatic) stretching	3101cm^{-1}
5	C=N	1658 cm^{-1}

INFERENCE

No shift and no disappearance of characteristic peaks suggesting that there is no interaction between the drugs and also with the excipients in the final formulation.

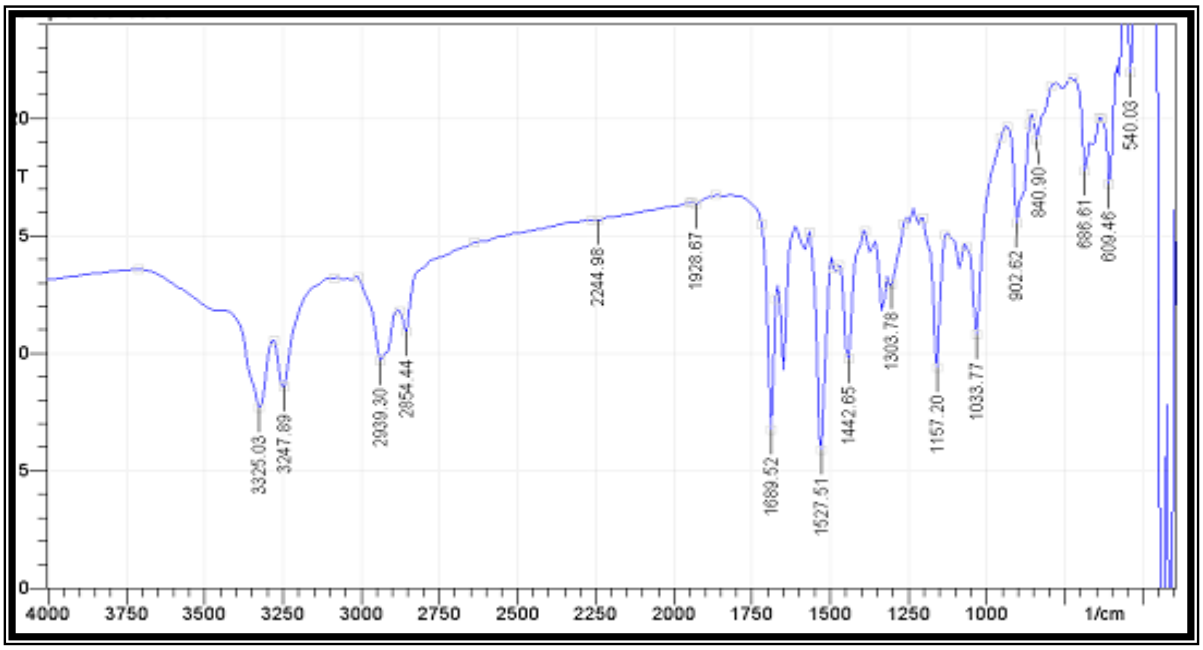


Fig 18: FTIR of Glipizide and Ethyl cellulose

Table 15: IR Spectral Interpretation of Glipizide and Ethyl cellulose

S.NO	Functional group	Observed peak
1	N-H (Primary amine) stretching	3325 cm^{-1}
2	C=O (Carboxylic acid) stretching	1689 cm^{-1}
3	C-H (alkane) stretching	2854 cm^{-1}

INFERENCE

No shift and no disappearance of characteristic peaks suggesting that there is no interaction between the drugs and also with the excipients in the final formulation.

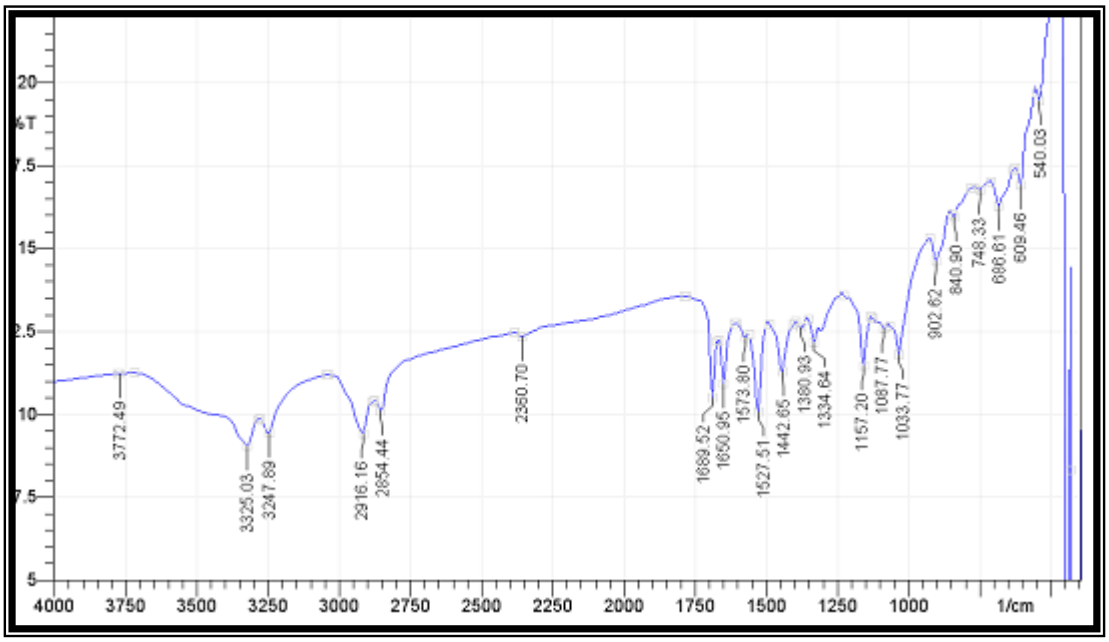


Fig 19: FTIR of Glipizide and HPMC K 100 M

Table 16: IR Spectral Interpretation of Glipizide and HPMC K 100 M

S.NO	Functional group	Observed peak
1	O-H (Carboxylic acid) stretching	3325 cm^{-1}
2	C=O (Carboxylic acid) stretching	1650 cm^{-1}
3	C-H (alkane) stretching	2916 cm^{-1}
4	C=N	1689 cm^{-1}

INFERENCE

No shift and no disappearance of characteristic peaks suggesting that there is no interaction between the drugs and also with the excipients in the final formulation.

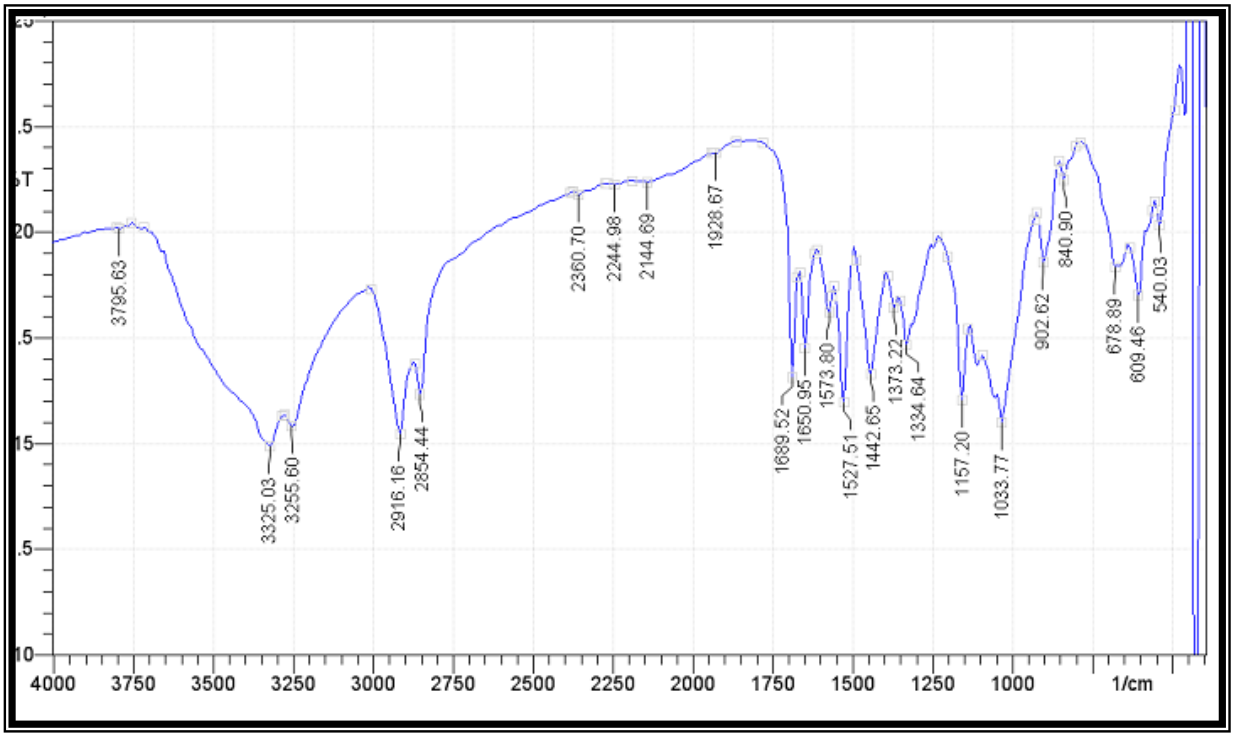


Fig 20: FTIR of optimized bilayer formulation

Table 17: IR Spectral Interpretation of optimized bilayer formulation

S.NO	Functional group	Observed peak
1	O-H (Carboxylic acid) stretching	3325 cm^{-1}
2	C=O (Carboxylic acid) stretching	1650 cm^{-1}
3	N-H (secondary amine) stretching	3255 cm^{-1}
4	C-H (alkane) stretching	2916 cm^{-1}
5	C=N	1689 cm^{-1}

INFERENCE

No shift and no disappearance of characteristic peaks suggesting that there is no interaction between the drugs and also with the excipients in the final formulation.

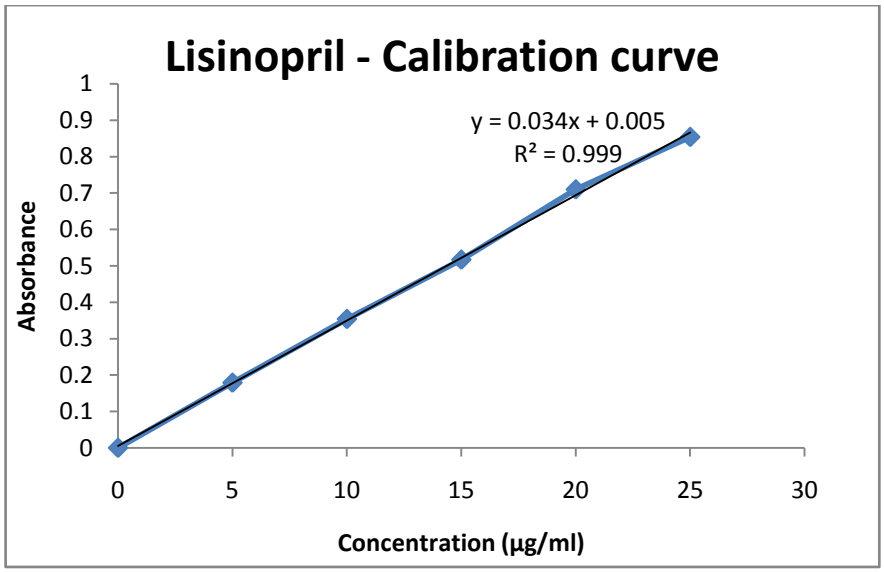
1. CALIBRATION CURVE FOR LISINOPRIL

The data for calibration curve of Lisinopril in 0.1M HCl is shown in table 21 and calibration curve shown in Fig 18.

Table 21: Data for calibration curve of Lisinopril in 0.1M HCl

S.NO	Concentration (µg/ml)	Absorbance at λ_{207nm}
1	0	0
2	5	0.179
3	10	0.354
4	15	0.517
5	20	0.710
6	25	0.854

Fig 18: Calibration Curve of Lisinopril



It was found that the solution of Lisinopril in 0.1M HCl show linearity (R^2 = 0.999) at concentrations of 5-25 (µg/ml) and obey Beer Lambert Law.

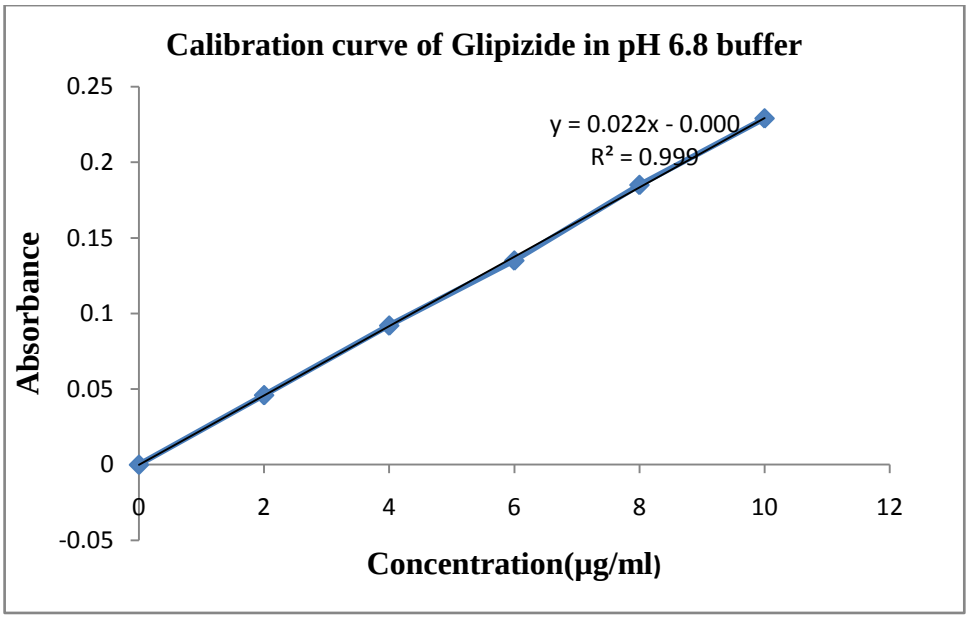
2. CALIBRATION CURVE FOR GLIPIZIDE

The data for calibration curves of Glipizide in pH 6.8 phosphate buffer is shown in table 22 and the calibration curve shown in Fig 19.

Table 22: Data for calibration curve of Glipizide in pH 6.8 buffer

S.NO	Concentration (µg/ml)	Absorbance at λ_{276nm}
1	0	0
2	2	0.046
3	4	0.092
4	6	0.135
5	8	0.185
6	10	0.229

Fig 19: Calibration curve of Glipizide in pH 6.8 buffer



It was found that the solution of Glipizide in pH 6.8 phosphate buffer show linearity (R^2 = 0.999) at concentrations of 2-10 (µg/ml) and obey Beer and Lambert Law.

FOR IR FORMULATION

PRECOMPRESSION STUDY

The API and the formulated blends were evaluated for precompression parameters.

Table 23: Pecompression study of API and formulated blends

API and formulation	Bulk density g/cm^3	Tapped densit g/cm^3	Compressibili Index (%)	Hausner's Ratio	Angle of Repose(Degree
Lisinopril	0.2947 ± 0.0142	0.3583 ± 0.0209	17.6901 ± 0.8437	1.2150 ± 0.0124	30° 97' ± 0.2654
L-1	0.2636 ± 0.0113	0.3343 ± 0.0182	21.0989 ± 0.9126	1.2675 ± 0.0146	32° 04' ± 0.4172
L-2	0.2783 ± 0.0126	0.3583 ± 0.0209	22.274 ± 1.0083	1.2868 ± 0.0167	30° 96' ± 1.6669
L-3	0.2947 ± 0.0142	0.3846 ± 0.0243	23.5844 ± 1.1246	1.3089 ± 0.0192	32° 83' ± 1.5391

Mean ± S.D (n=3)

The bulk density of the IR blends ranged from 0.2636 – 0.2947 g/cm^{3}and the tapped density ranged from 0.3343 – 0.3846 g/cm^3. The compressibility index of the IR blends ranged from 21.09% - 23.58% and Hausner's ratio ranged from 1.2675 – 1.3089. The angle of repose of the IR blends ranged from 30° 96'- 32° 83'. The formulated blends showed good flow property, so wet granulation technique was used for preparing IR granules of Lisinopril.

The IR granules were evaluated for bulk density, tapped density, compressibility index, Hausner's ratio and Angle of repose. The results are given below.

Table 24: Precompression study of formulated IR granules

Formulation	Bulk density g/cm^3	Tapped densit g/cm^3	Compressibility index (%)	Hausne's ratio	Angle of Repose (Degree)
L-1	0.2783 ± 0.0126	0.3583 ± 0.0209	22.27 ± 1.0088	1.2868 ± 0.0167	32° 61' ± 1.2739
L-2	0.2783 ± 0.0126	0.3861 ± 0.0243	27.83 ± 1.2578	1.3862 ± 0.0242	31° 40 ± 1.0210
L-3	0.2947 ± 0.0142	0.3583 ± 0.0209	17.68 ± 0.8416	1.1687 ± 0.0763	31° 64 ± 0.6613

Mean ± S.D (n=3)

The bulk density of the IR granules ranged from 0.2783 – 0.2947 $g/cm^3$and tapped density ranged from 0.3583 – 0.3861 g/cm^3. The compressibility index of the IR granules ranged from 17.68% - 27.83% and Hausner's ratio ranged from 1.1687 – 1.3862. The angle of repose of the IR granules ranged from 31° 40' - 32° 61'. The formulated IR granules showed good flow property.

FORMULATION DEVELOPMENT

Preparation of IR tablets of Lisinopril

Wet granulation technique was employed for the formulation of IR granules of Lisinopril. Three formulations of immediate release layer of Lisinopril (L1, L2 and L3) were prepared using sodium starch glycolate (super disintegrant) in three different ratios. The granules were compressed using 10 station tablet compression machine using 10/32 punches.

POST COMPESSION STUDY FOR TABLETS

UNIFORMITY OF WEEIGHT

The uniformity of weight of the formulated tablets is given in table 25.

Table 25 : Unifomity of weight of the formulated tablets

Formulation	**Uniformity of weight (mg)**
Specified limit	**189.8 – 206.4**
L-1	195.34 ± 0.8935
L-2	197.84 ± 0.5678
L-3	198.68 ± 0.4791

Mean ± S.D (n=5)

The tablets comply with the test for uniformity of weight.

TABLET THICKNESS AND DIAMETER

The thickness and diameter of the formulated tablets is given in table 26.

Table 26: Thickness and diameter of formulated tablets

Formulation	**Diameter (mm)**	**Thickness (mm)**
Specified limit	**4.5 – 5.0**	**2.5 – 3**
L-1	4.88 ± 0.0748	2.7 ± 0.2449
L-2	4.84 ± 0.0489	2.84 ± 0.1019
L-3	4.92 ± 0.0748	2.98 ± 0.04

Mean ± S.D (n=5)

The tablets were found to be uniform in thickness and diameter.

HARDNESS

The hardness of the formulated tablets is given in table 27.

Table 27: Hardness of formulated tablets

Formulation	**Hardness (kg/cm^2)**
Specified limit	**3.5 – 4**
L-1	3.88 ± 0.0748
L-2	3.9 ± 0.0894
L-3	3.96 ± 0.12

Mean ± S.D (n=5)

All the formulated tablets showed sufficient mechanical strength to resist the transportation.

FRIABILITY

The friability of the formulated tablets is given in table 28.

Table 28: Friability of formulated tablets

Formulation	**% Friability**
Specified limit	**Not more than 1.0%**
L-1	0.6277 ± 0.0912
L-2	0.3347 ± 0.0392
L-3	0.7076 ± 0.0712

Mean ± S.D (n=3)

The percentage friability of all the formulations was within the acceptable limits. i.e not more than 1%.

DRUG CONTENT

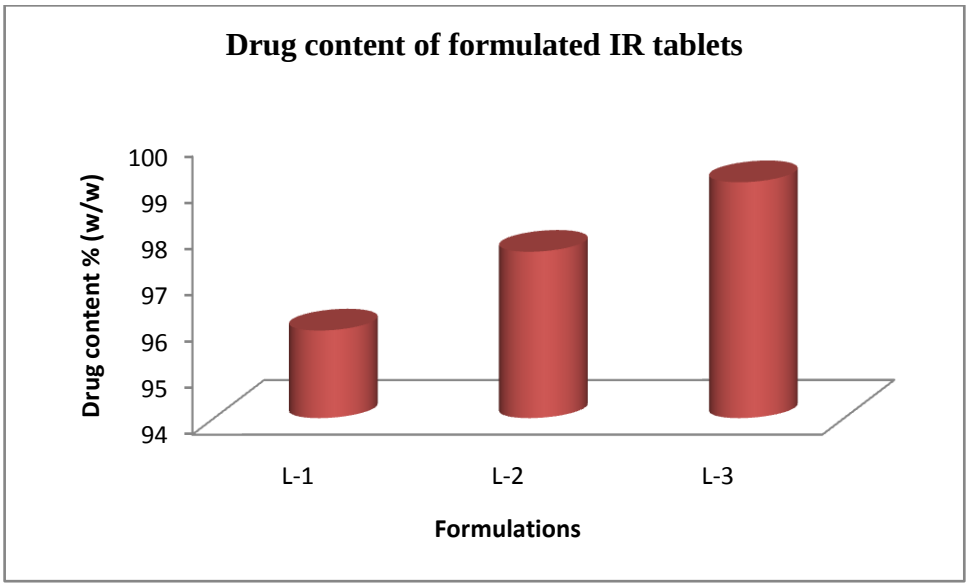
The drug content of the IR tablets is given in table 29.

Table 29: Drug content of formulated IR tablets

Formulation	**(% w/w) Drug Content**
Specified limit	**90 – 110%**
L-1	95.89 ± 0.9093
L-2	97.59 ± 0.4994
L-3	99.09 ± 0.4532

Mean ± S.D (n=3)

Fig 20: Drug content of IR tablets



The drug contents of all three IR formulations were found to be within the limit. i.e the drug content was not less than 90% and not more than 110% (as per IP: 2010).

DISINTEGRATION TIME

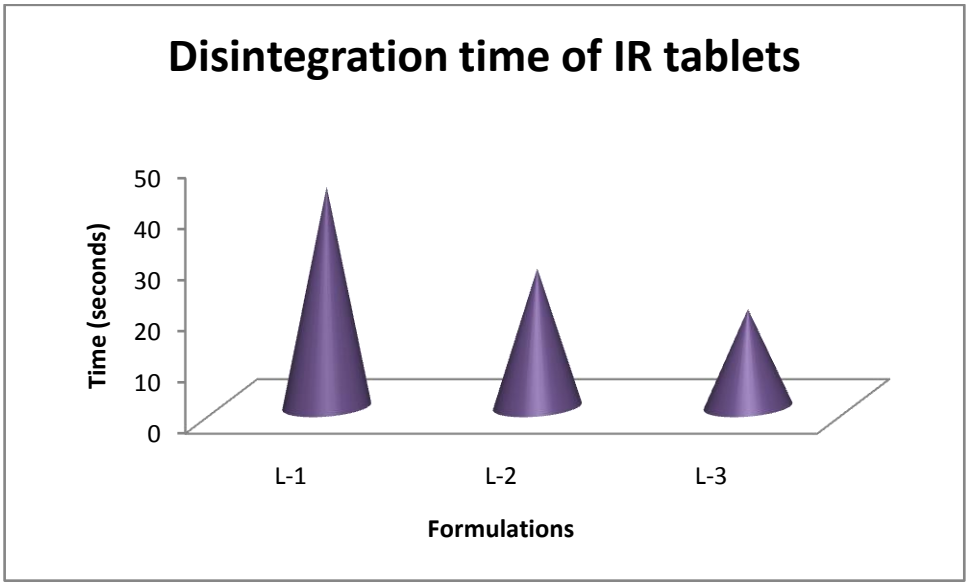
The disintegration time of the IR tablets is given in table 30.

Table 30: Disintegration time of IR tablets

Formulation	Disintegration time (seconds)
L-1	43.02 ± 0.8369
L-2	27.05 ± 0.8090
L-3	19.07 ± 0.8492

Mean ± S.D (n=3)

Fig 21: Disintegration time of IR tablets



The disintegration time of the IR tablets ranged from 43.02 seconds to 19.07seconds. The disintegration time of the IR tablets containing 8% sodium starch glycolate was found to have optimum disintegration time (19.07seconds) for IR tablets.

IN VITRO DISSOLUTION STUDY

The *in vitro* dissolution of immediate release formulations of Lisinopril is shown in table 31 and Fig 22.

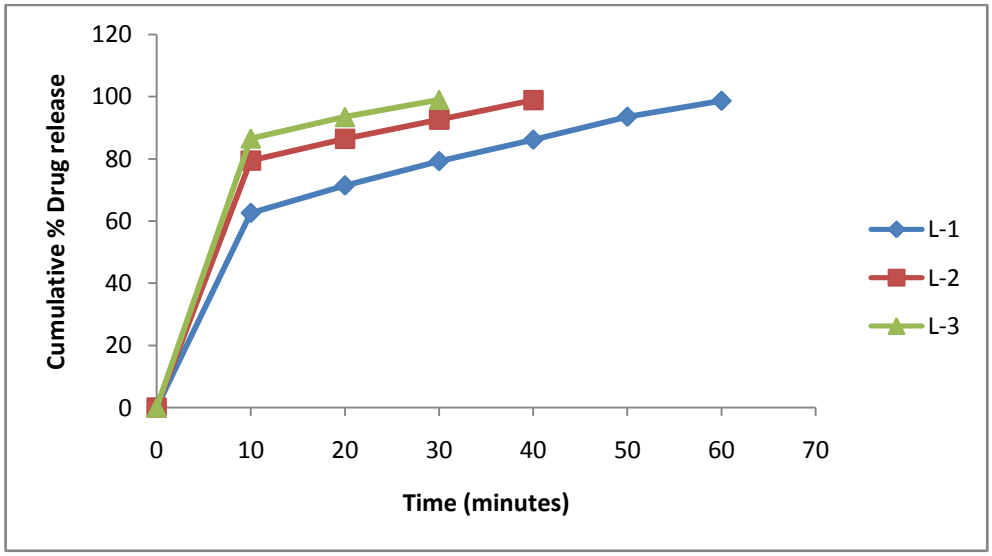
Table 31: *In vitro* dissolution study of Immediate release tablets

Time(minutes)	Cumulative % Drug release		
	L-1	L-2	L-3
0	0 ± 0.0000	0 ± 0.0000	0 ± 0.0000
10	62.6 ± 0.7761	79.42 ± 0.5316	86.58 ± 0.7331
20	71.43 ± 0.8859	86.43 ± 0.5461	93.49 ± 0.5218
30	79.26 ± 0.7318	92.63 ± 0.8941	98.74 ± 0.5925
40	86.14 ± 0.8942	98.87 ± 0.5041	
50	93.54 ± 0.9474		
60	98.66 ± 0.5470		

Mean ± S.D (n=3)

The *in vitro* dissolution study of IR tablets showed that 8% concentration of SSG was found to be optimum for immediate release of Lisinopril. The 4% and 6% concentration of SSG was found to be releasing the drug slowly when compared to 8% SSG. The 8% concentration of SSG released 98.94% at the end of 30minutes. Therefore formulation L-3 was optimized and selected for final bilayer tablets.

Fig 22*: In vitro* dissolution study of IR tablets of Lisinopril



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FOR SR TABLETS

PRECOMPRESSION STUDY

The API and the formulated blends of SR were evaluated for precompression parameters. The results are given in table 32.

Tablet 32: Precompresson study of API and formulated blends

API and formulation	**Bulk density g/cm^3**	**Tapped Density g/cm^3**	**Compressibili Index (%)**	**Hausner's ratio**	**Angle of Repose(Degree**
Glipizide	0.2636 ± 0.0113	0.3572 ± 0.0222	26.36 ± 1.1435	1.3540 ± 0.02658	28° 66' ± 0.9203
G-1	0.2503 ± 0.0102	0.3343 ± 0.01822	25.05 ± 1.0133	1.3344 ± 0.0180	31° 34' ± 0.3390
G-2	0.2503 ± 0.0102	0.2947 ± 0.0142	15.02 ± 0.6169	1.1769 ± 0.0085	31° 40 ± 1.0210
G-3	0.2636 ± 0.0113	0.3133 ± 0.0160	15.82 ± 0.6901	1.1881 ± 0.0097	32° 58 ± 1.2364
G-4	0.2783 ± 0.0126	0.3343 ± 0.0182	16.70 ± 0.7514	1.2007 ± 0.0108	31° 40 ± 0.9566
G-5	0.2636 ± 0.0113	0.2947 ± 0.0160	15.82 ± 0.6899	1.1179 ± 0.0059	32° 83 ± 0.2864

Mean ± S.D (n=3)

The bulk density of the SR blends ranged from 0.2503 – 0.2783 g/cm^{3}and the tapped density ranged from o.2947 -0.3572 g/cm$^{3.}$ The compressibility index ranged from 15.82 – 26.36% and Hausner's ratio ranged from 1.1179 – 1.3540.

The angle of repose of the SR blend ranged from 28° 66' - 32° 83. The formulated blends showed good flow property so wet granulation technique was used for preparing SR granules of Glipizide. The SR granules were evaluated for bulk density, tapped density, compressibility index, Hausner's ratio and angle of repose. The results are given in table 33.

Table 33: Precompression study of sustained release granules

Formulation	Bulk density g/cm^3	Tapped densit g/cm^3	Compressibili Index (%)	Hausner's ratio	Angle of Repose
G-1	0.2783 ± 0.0126	0.3583 ± 0.0209	22.27 ± 1.0088	1.2868 ± 0.0167	31° 34 ± 0.3390
G-2	0.3133 ± 0.0160	0.3861 ± 0.0243	18.79 ± 0.9600	1.2316 ± 0.0145	31° 25 ± 0.8739
G-3	0.2503 ± 0.0102	0.2947 ± 0.0142	15.02 ± 0.6169	1.1769 ± 0.0085	31° 88' ± 0.3253
G-4	0.2636 ± 0.0113	0.3133 ± 0.0160	15.82 ± 0.6901	1.1881 ± 0.0097	31° 17 ± 0.6636
G-5	0.2783 ± 0.0126	0.3343 ± 0.0182	16.70 ± 0.7514	1.2007 ± 0.0108	31° 73' ± 0.4286

Mean ± S.D (n=3)

The bulk density of the SR granules ranged from 0.2503 – 0.2783 g/cm^{3}and the tapped density ranged from 0.2947 -0.3583 g/cm^3. the compressibility index ranged from 15.02 – 22.27% and Hausner's ratio ranged from 1.1769 – 1.2868. The angle of repose of the SR granules ranged from 31° 17' - 31° 88'. The formulated SR granules showed good flow property.

FORMULATION DEVELOPMENT

Wet granulation technique was employed for the formulation of SR granules of Glipizide. Five batches of SR granules were prepared by using hydrophilic polymer HPMC K100M and hydrophobic polymer EC in varying proportions. The formulations were compressed on a 10station tablet compression machine.

POST COMPRESSION STUDY

UNIFORMITY OF WEIGHT

The uniformity of weight of the formulated tablets is given in table 34.

Table 34: Uniformity of weight of the formulated tablets

Formulation	**Uniformity of weight (mg)**
Specified limit	**240-270**
G-1	251.32 ± 0.9579
G-2	261.38 ± 0.8653
G-3	254.38 ± 0.5715
G-4	254.00 ± 0.8993
G-5	254.4 ± 0.9392

Mean ± S.D (n=5)

The tablet complies with the test for uniformity of weight.

TABLET THICKNESS, DIAMETER AND HARDNESS

The thickness, diameter and hardness of the formulated tablets are given in table 35.

Table 35: Thickness, Diameter and Hardness of formulated tablets

Formulation	**Thickness (mm)**	**Diameter (mm)**	**Hardness(Kg/cm^2)**
Specified limit	**2.5 – 3.5**	**4.5 – 5.5**	**4-6**
G-1	2.88 ± 0.3187	4.8 ± 0.2449	4.92 ± 0.1469
G-2	2.82 ± 0.1939	4.82 ± 0.1469	5.06 ± 0.1356
G-3	2.88 ± 0.0748	4.86 ± 0.1019	5.2 ± 0.1095
G-4	3.08 ± 0.1720	4.94 ± 0.1356	5.24 ± 0.0489
G-5	3.02 ± 0.1166	4.8 ± 0.1095	5 ± 0.0894

Mean ± S.D (n=5)

The tablets were found to be uniform in thickness, diameter and hardness.

FRIABILITY

The friability of formulated tablet is given in table 36.

Table 36: Friability of formulated tablets

Formulation	**Friability**
Specified limit	**Not more than 1.0%**
G-1	0.7923 ± 0.0526
G-2	0.8273 ± 0.0600
G-3	0.7019 ± 0.0646
G-4	0.9153 ± 0.0527
G-5	0.6517 ± 0.0498

Mean ± S.D (n=3)

The percentage friability of all formulations were within the acceptable limits. i.e. not less than 1%.

DRUG CONTENT

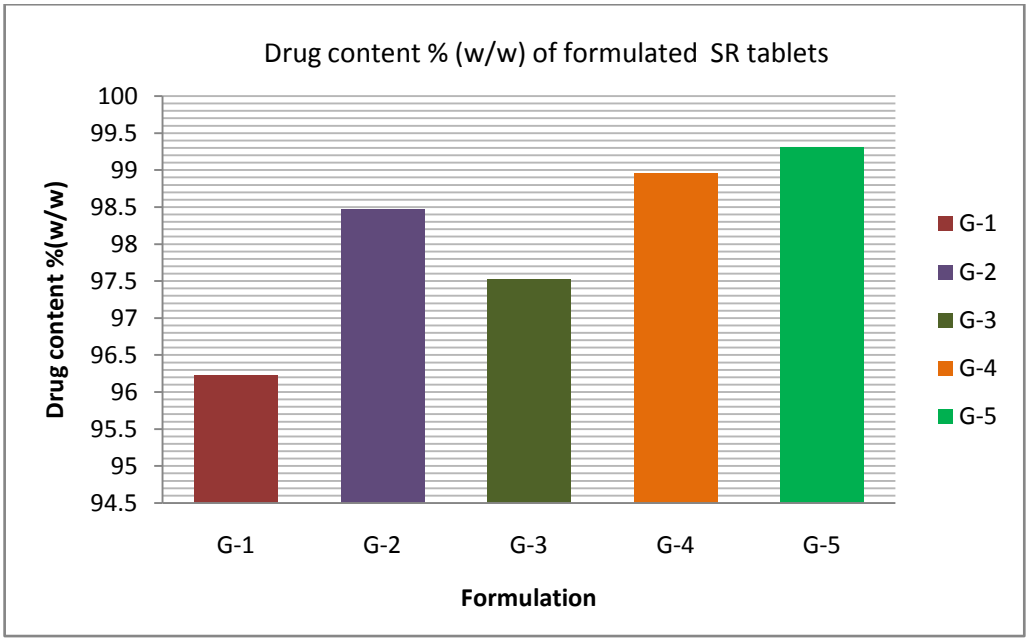
The percentage drug content values of the SR tablets are given in table table 37 and Fig 23.

Table 37: Drug content (%w/w) of formulated SR tablets

Formulation	**Drug content (%w/w)**
Specified limit	**90-110%**
G-1	96.22 ± 0.8538
G-2	98.47 ± 0.6375
G-3	97.52 ± 0.9785
G-4	98.95 ± 0.2174
G-5	99.30 ± 0.2833

Mean ± S.D (n=3)

Fig 23: Percentage drug content of SR tablets



The drug contents of all five SR formulations were found to be within the limit. i.e the drug content was not less than 90% and not more than 110% (as per IP: 2010)

IN VITRO DISSOLUTION STUDY OF SR TABLETS

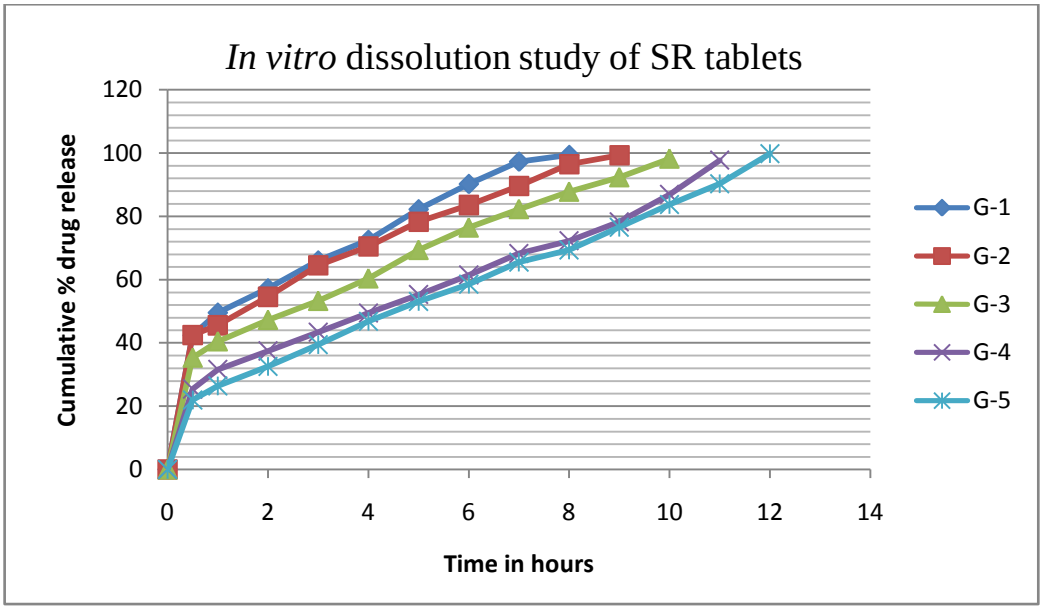
The *in vitro* dissolution study of SR tablets is given in table 38 and Fig 24.

Table 38: *In vitro* dissolution study of SR tablets

Time (minutes)	**G-1**	**G-2**	**G-3**	**G-4**	**G-5**
0	0 ± 0.0000	0 ± 0.0000	0 ± 0.0000	0 ± 0.0000	0 ± 0.0000
30	42.38 ± 0.5646	42.47 ± 0.7855	35.34 ± 0.8794	25.42 ± 0.7870	21.97 ± 0.5142
60	49.55 ± 0.4883	45.57 ± 0.5358	40.50 ± 0.8211	31.59 ± 0.7200	26.37 ± 0.8169
120	57.22 ± 0.8032	54.56 ± 0.8515	47.28 ± 0.9883	37.44 ± 0.7268	32.59 ± 0.7453
180	66.05 ± 0.6513	64.53 ± 0.6033	53.28 ± 0.8118	43.36 ± 0.9340	39.45 ± 0.8172
240	72.56 ± 0.6287	70.50 ± 0.6697	60.38 ± 0.7189	49.45 ± 0.5832	46.84 ± 0.9150
300	82.24 ± 0.6975	78.31 ± 0.7524	69.37 ± 0.7451	55.28 ± 0.8374	53.10 ± 1.3540
360	90.25 ± 0.7721	83.58 ± 0.5930	76.45 ± 0.9353	61.45 ± 0.7162	58.57 ± 0.9360
420	97.39 ± 0.9471	89.64 ± 0.8051	82.28 ± 0.7587	68.25 ± 0.9554	65.53 ± 1.3214
480	99.42 ± 0.3890	96.49 ± 0.9182	87.78 ± 0.8722	72.28 ± 0.9393	69.40 ± 0.7156
540		99.31 ± 0.2246	92.35 ± 0.9594	78.26 ± 0.8334	76.54 ± 0.8234
600			98.23 ± 0.4325	86.92 ± 0.8123	83.78 ± 0.7659
660				97.73 ± 0.7683	90.34 ± 0.6785
720					99.82 ± 0.6895

Mean ± S.D (n=3)

Fig 24: In vitro dissolution study of S tablets



The results of In vitro dissolution study of SR tablets showed that

- The formulation G1 containing EC(20%) had released the drug 99.42% in 8 hours.
- The formulation G2 containing HPMC K100M (20%) had released the drug 99.31% in 9 hours.
- The formulation G3 containing EC and HPMC K100M (1:1) had released the drug 98.23% in 10 hours. The release of the drug was retarded when compared to the formulation G2.
- The formulation G4 containing EC and HPMC K100 M (1:2). The release of the drug (97.73% in 11 hrs) was retarded when compared to G3.
- The formulation G5 containing EC and HPMC K100M (1:4). The release of the drug (99.82% in 12 hrs) was retarded when compared to formulation G4.
- Based on the comparative release profile, formulation G5 was selected for the final bilayer tablets.

FORMULATION DEVELOPMENT

PREPARATION OF BILAYER TABLETS

1. Optimized immediate layer of Lisinopril was prepared by wet granulation method.

2. Optimized sustained release layer of Glipizide was prepared by wet granulation method.

The granules were compressed on 10 station bilayer tablet compression machine.

POST COMPRESSION STUDY OF BILAYER TABLETS

Table 39: Post compression study of Bilayer tablets

Parameters	**Bilayer tablet**
Uniformity of weight (mg)	448.18 ± 0.8863
Thickness (mm)	5.88 ± 0.0748
Diameter (mm)	4.91 ± 0.1065
Hardness (kg/cm^2)	5.82 ± 0.1648
Friability (%)	0.3692 ± 0.0613
Drug content* (simultaneous estimation method) 1. Lisinopril 2. Glipizide	 1. 98.26 ± 0.5157 2. 93.32 ± 0.8906

Mean ± S.D (n=5) ***Mean ± S.D (n=3**

IN VITRO DISSOLUTION STUDY OF LISINOPRIL IN BILAYER TABLET

The *in vitro* dissolution study of drugs in bilayer tablets is given in table 40, 41 and Fig 25, 26.

Table 40: The *in vitro* dissolution study of Lisinopril in bilayer tablet

Time (minutes)	**% Drug release**
0	0 ± 0.0000
10	79.27 ± 0.2236
20	90.15 ± 0.1342
30	98.74 ± 0.1855

Mean ± S.D (n=3)

Fig 25:The *in vitro* dissolution study of Lisinopril in bilayer tablet

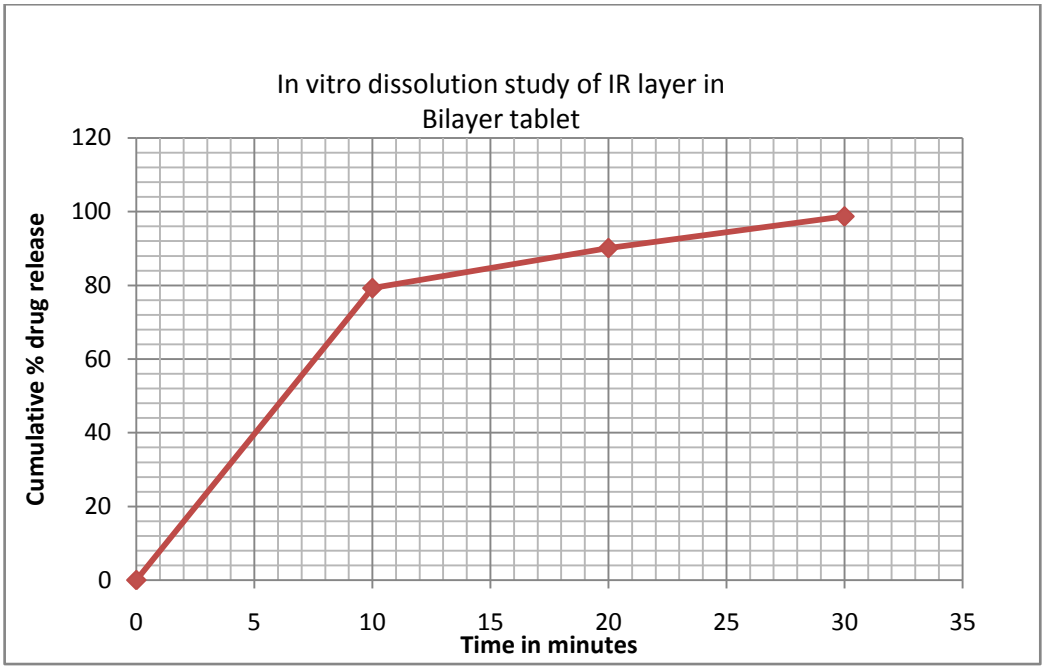
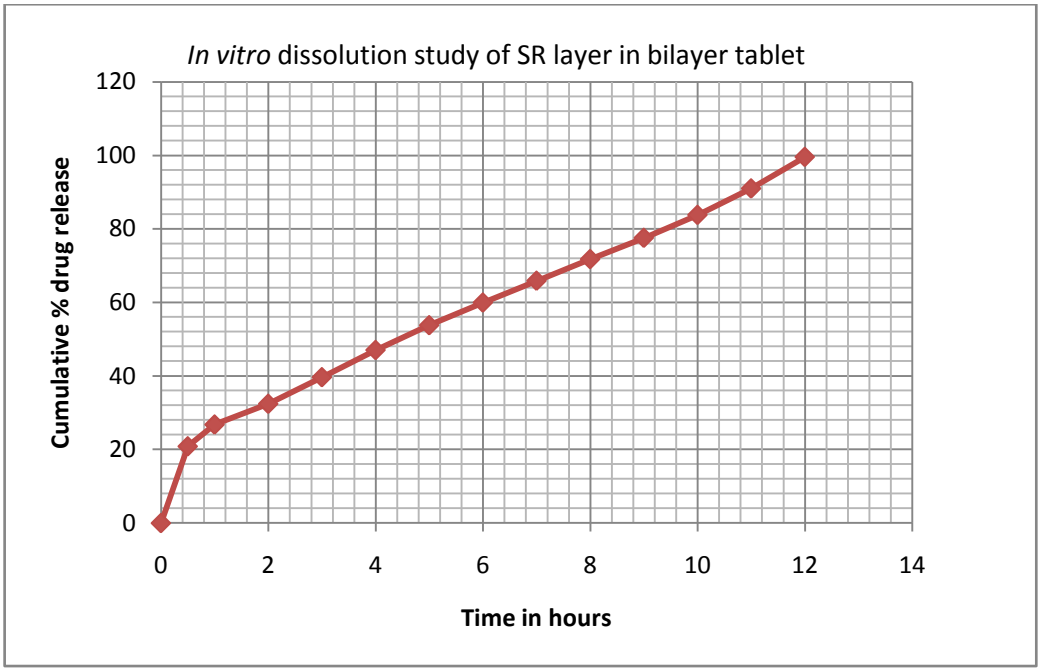


TABLE 41*: IN VITRO* DISSOLUTION STUDY OF GLIPIZIDE IN BILAYER TABLET

Time (minutes)	% Drug release
0	0 ± 0.0000
30	20.87 ± 0.1885
60	26.79 ± 0.3091
120	32.43 ± 0.1114
180	39.66 ± 0.2315
240	47.05 ± 0.1586
300	53.79 ± 0.4348
360	59.95 ± 0.3069
420	65.88 ± 0.5307
480	71.76 ± 0.3943
540	77.54 ± 0.4231
600	83.78 ± 0.3465
660	90.97 ± 0.2341
720	99.54 ± 0.1994

Mean ± S.D (n=3)

Fig 26: *In vitro* dissolution study of Glipizide in bilayer tablet



IN VITRO RELEASE KINETICS

In order to describe the release kinetics the values obtained from *in vitro* dissolution of Glipizide from bilayer tablets were fitted in various kinetic dissolution models like zero order, first order, Higuchi, Korsmeyer Peppas and Hixson Crowell respectively. The various parameters like the time exponent (n), the release rate constant (k) and the regression co-efficient (R^2) were also calculated. In a set of data, the model showing the highest value of $R^2$was taken as the best fit model. The results are given in table 42.

Table 41: *In vitro* release kinetics of bilayer tablets

Time (hours)	%Cum drug release	%Cum drug Remaining (g)	Log % Cum Drug Remaining (g)	Square Root of time	Log time	Log % Cum drug release	Cube root Of %drug Remaining (g)
0	0	100	2	0	-∞	-∞	4.6415
0.5	20.87	79.13	1.8983	0.7071	0.3010	1.3195	4.293
1	26.79	73.21	1.8645	1.0	0.0	1.4279	4.1833
2	32.42	67.58	1.8298	1.4142	0.3010	1.5108	4.0732
3	39.66	60.34	1.7806	1.7320	0.4771	1.5983	3.9222
4	47.05	52.95	1.7238	2.0	0.6020	1.6725	3.7551
5	53.79	46.21	1.6647	2.2360	0.6989	1.7307	3.5884
6	59.95	40.05	1.6026	2.4494	0.7781	1.7777	3.4213
7	65.88	34.12	1.5330	2.6457	0.8450	1.8187	3.2434
8	71.76	28.24	1.4508	2.8284	0.9030	1.8558	3.0452
9	77.54	22.46	1.3514	3.0	0.9542	1.8895	2.8214
10	83.78	16.22	1.2100	3.1622	1.0	1.9231	2.5313
11	90.97	9.03	0.9556	3.3166	1.0413	1.9588	2.0823
12	99.54	0.46	0.3372	3.4641	1.0791	1.9979	0.7719

Fig 27: Zero order release kinetics

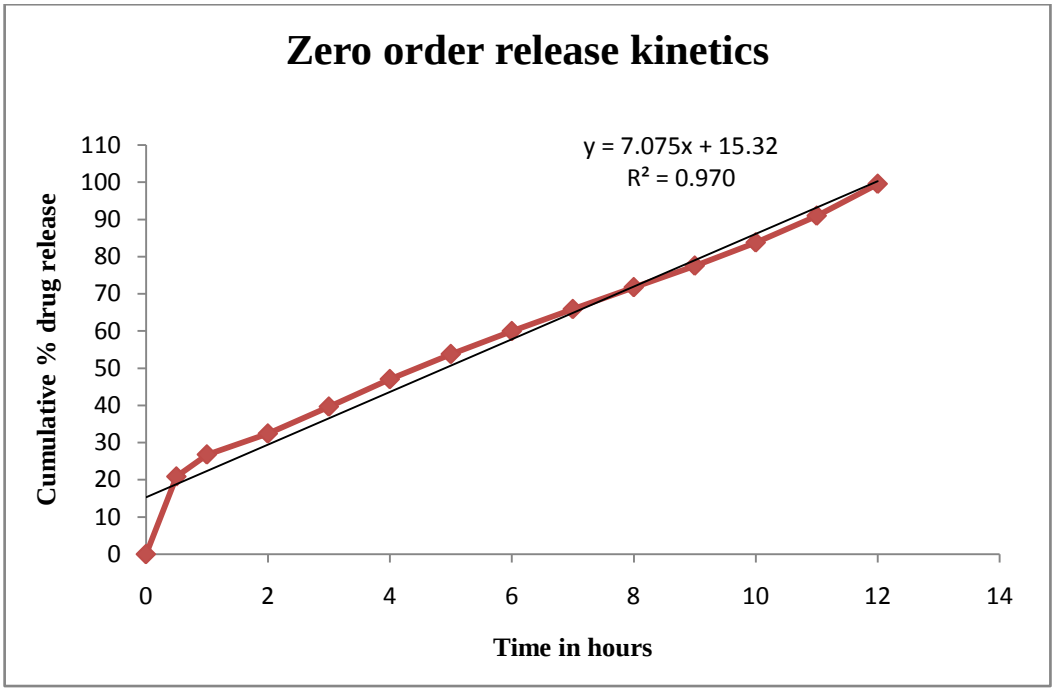


Fig 28: First order release kinetics

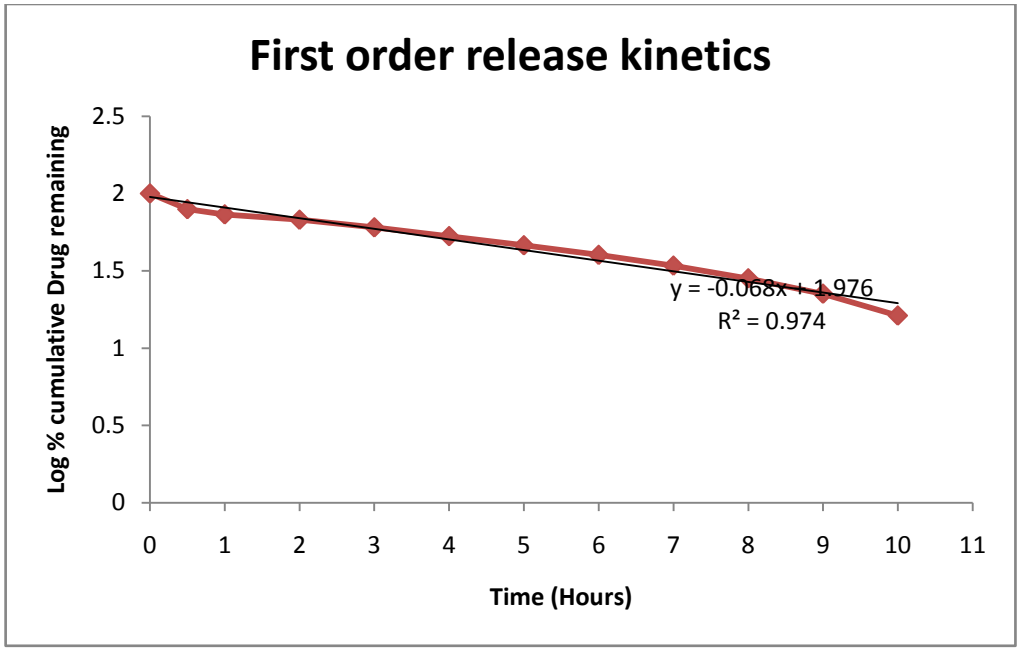


Fig 29: Higuchi diffusion kinetics

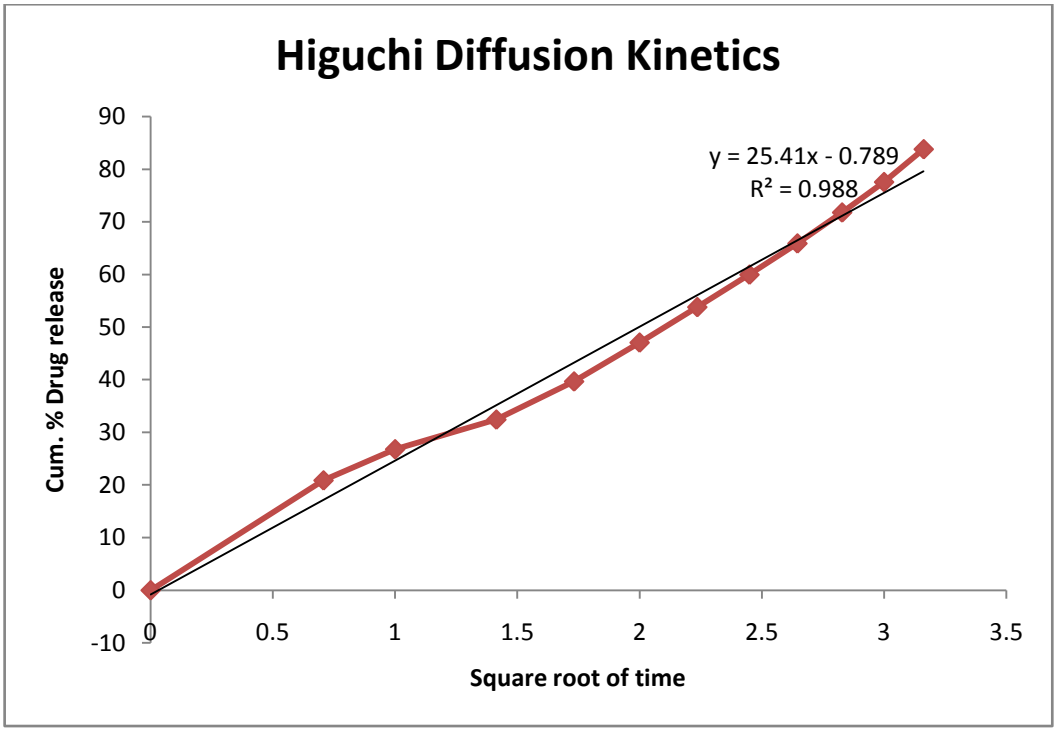


Fig 30: Korsmeyer Peppas equation

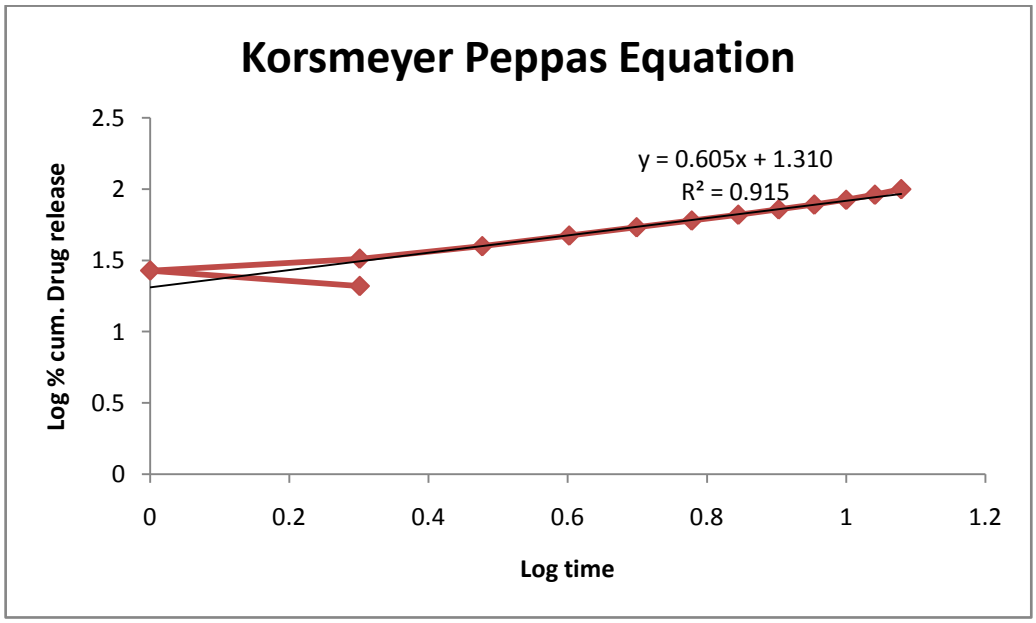


Fig 31: Hixson Crowell cube root equation

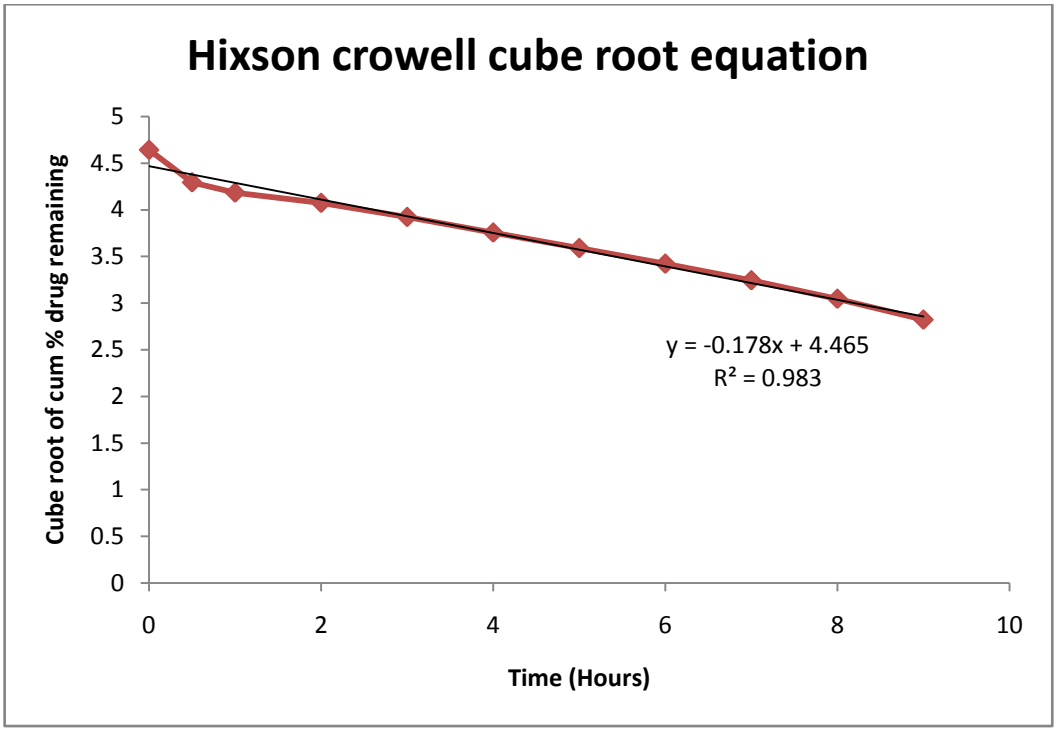


Table 42 :Data of various parameters of model fitting for Glipizide release from the optimized bilayer formulation

Formulation	Zero order	First order	Higuchi	Korsmeyer Peppas		Hixson Crowel
Optimised formulation	R^2	R^2	R^2	R^2	n	R^2
	0.970	0.974	0.988	0.915	0.605	0.983

Determination of drug release mechanism of optimised bilayer tablets

- The order of release was found to be first order, in which R^2value was closer to 1 than the value of $R^2$of the first order equation.
- In Higuchi diffusion kinetics the R^2value was near to 1. So it was concluded that the optimized formulation follows Higuchi diffusion mechanism.
- The n value of Korsmeyer Peppas equation was found to be 0.605, from that it was concluded that the release followed nonfickian transport.

- Swelling hydration of the polymer matrix, dissolution of the drug in the polymer matrix, and diffusion of the drug through the polymer matrix and surface erosion of the matrix also plays role in the drug release. The results showed that the formulation followed first order release.

STABILITY STUDIES

The optimised bilayer tablets were subjected to stability studies and the results are given in table 43 and 44.

Table 43: Stability study of physical parameters of the optimized bilayer tablets

Parameters	Initial	1st month	2nd month	3rd month
Uniformity of weight	448.18 ± 0.8863	448.79 ± 0.4443	448.92 ± 0.4608	448.94 ± 0.4108
Thickness (mm)	5.88 ± 0.0748	5.88 ± 0.0748	5.88 ± 0.0748	5.88 ± 0.0748
Diameter (mm)	4.91 ± 0.1065	4.91 ± 0.1065	4.91 ± 0.1065	4.91 ± 0.1065
Hardness (kg/cm^2)	5.82 ± 0.1648	5.82 ± 0.1648	5.82 ± 0.1648	5.82 ± 0.1648
Friability (%)	0.3692 ± 0.0613	0.2948 ± 0.0038	0.3172 ± 0.0033	0.3220 ± 0.0017

Table 44: Assay and dissolution profile of bilayer tablet

Time interval (month)	Drug content (% w/w)		Cumulative % drug release	
	Lisinopril	Glipizide	Lisinopril (at the end of 30mins)	Glipizide (at the end 12hours)
Initial	98.26 ± 0.5157	93.32 ± 0.8906	98.74 ± 0.1855	99.54 ± 0.1994
1st month	98.84 ± 0.3024	93.87 ± 0.1835	98.81 ± 0.2245	99.21 ± 0.2290
2nd month	98.77 ± 0.3597	93.96 ± 0.2145	98.65 ± 0.3365	99.27 ± 0.3351
3rd month	98.91 ± 0.3512	94.02 ± 0.2160	98.71 ± 0.3447	99.17 ± 0.3108

Summary & Conclusion

11. SUMMARY AND CONCLUSION

SUMMARY

The present work involves the formulation development, optimization and *In-vitro* evaluation of bilayer tablet containing Lisinopril in the immediate release layer and Glipizide in the sustained release layer, using sodium starch glycolate as a super disintegrant for the immediate release layer and the hydrophilic matrix HPMC K100M, hydrophobic matrix Ethyl cellulose are used in the sustained release layer.

Bilayer tablet showed as initial burst effect to provide dose of immediate release layer Lisinopril to control the blood pressure level and the sustained release of Glipizide for 24hours to control the blood glucose level. The developed formulation shows an alternative to the conventional dosage form for the treatment of diabetes along with diabetic hypertension and nephropathy.

- Under the preformulation studies, API (Active Pharmaceutical Ingredient) characterization and drug-excipient compatibility studies were carried out. The API characterization showed compliance with the drug characteristics.

- The polymers and other excipients were selected based on the satisfying results produced during drug-excipient compatibility studies to develop the final formulation.

- Immediate and sustained release tablets were formulated by wet granulation method because of the poor flow property of the blends.

- The formulated granules were evaluated for precompression studies which showed that the flow property was good.

- The formulated tablets were found to be within the limits with respect to uniformity of weight, hardness, thickness, diameter and friability.

- The disintegration time of IR tablets containing SSG 8% was found to be optimum.

- The drug content of the formulated IR and SR tablets were found to be within limits.

- Based on the *in vitro* dissolution studies of IR tablets, formulation L3 was optimised and selected for final bilayer tablets.

- Based on the *in vitro* dissolution studies of SR tablets, formulation G5 containing EC and HPMC K100M (1:4). It released the drug 99.82% in 24hours. This formulation G5 was optimised and selected for bilayer tablets.

- The optimised IR and SR formulations were compressed into bilayer tablets.

- The formulated bilayer tablets were found to be within the limits with respect to uniformity of weight, hardness, thickness, diameter and friability.

- The drug content of the bilayer tablets were estimated by simultaneous estimation method and it was found to be within the pharmacopoeial limit.

- The in vitro dissolution studies of optimised bilayer tablets were released the drug upto 24 hours.

- The release kinetics of the optimized tablets showed that it follows zero order release kinetics. The release of the drug from the dosage form was found to be by dissolution and non fickian release.

- Stability studies of optimized bilayer tablets were carried out according to ICH guidlines. It indicated that the bilayer tablets are stable and does not show any significant changes in the physical characteristics, drug content and dissolution. The results obtained were found to be within the limits.

CONCLUSION

- Success of the *in vitro* drug release studies recommends the product for the further *invivo* studies, which may improve patient compliance.
- From the literature, it is seen that Lisinopril as an individual dosage form is used in the management of hypertension in patients with type I and type II diabetes mellitus. Glipizide is given as alone or in combination with other antidiabetic drugs in patients with type II diabetes.
- Lisinopril potentiate the effect of Glipizide. Hence the bilayer tablets of Lisinopril and Glipizide were used to improve patient compliance towards the effective management diabetes along with diabetic hypertension and nephropathy.
- Combination of Lisinopril as an immediate release layer and Glipizide as a sustained release layer reduces polytherapy to monotherapy.
- From the results, formulated bilayer tablet provides better *in vitro* release from immediate release layer as well as sustained release layer.
- The data obtained from *in vitro* release study for sustained release layer were fitted to various mathematical model like zero order, first order, Higuchi model and Peppas model. The results of mathematical model fitting of data obtained indicated that, the best fit model was zero order. Thus the release of the drug from the dosage form was found to be by dissolution and non fickian release.
- The stability studies indicated that the bilayer tablets are stable and does not show any significant changes.

FUTURE PLAN

- Scale up studies of the optimized formulation.
- *In vivo* studies and *in vivo- in vitro* correlation studies.
- Bioequivalence studies with the marketed formulations.

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